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VOLUME 78 NUMBER 1

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JULY 1946

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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GONOCOCCIC PERITONITIS OF THE UPPER PART OF THE ABDOMEN IN YOUNG WOMEN

(Phrenic Reaction, or Subcostal Syndrome of Stajano; Fitz-Hugh–Curtis Syndrome) Report of Cases of Three Patients Treated Successfully with Penicillin and a Summary of the Literature

MALCOLM M. STANLEY, M.D.
BOSTON

PERITONITIS of the upper part of the abdomen in young women occurring during the course of gonorrhea was first described as a definite syndrome in 1919 by Carlos Stajano, in a paper read before the Society of Obstetrics and Gynecology of Montevideo, Uruguay. In his subsequent publications [1] the clinical features of the acute stage of the disease were completely and graphically depicted. Little information of a clinical nature has been added since. Unfortunately, none of his work, printed in Spanish and French, was widely circulated in the United States. Hence it was not until 1930 that Curtis [2] called attention to the frequent coexistence of gonococcic salpingitis and "violin string" adhesions between the anterior surface of the liver and the anterior abdominal wall discovered at operation—conditions indicating, presumably, a chronic, healing or healed perihepatitis. Fitz-Hugh, in 1934,[3] described 3 cases in the acute stage, including 1 in which laparotomy was performed; in smears of the draining secretions from the wound gram-negative intracellular diplococci were seen. Since then numerous articles have appeared in the literature, and the clinical entity has been well documented.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

1. (*a*) Stajano, C.: La reacción frénica en ginecología, Semana méd. **27**: 243-248 (Aug. 19) 1920; (*b*) Réaction phrénique et infection génitale, Gynéc. et obst. **6**:44-48 (July) 1922. (*c*) Stajano, C., and Pouey, E.: Las reacciones del peritoneo supraceliaco de origen genital: Las reacciones precoces. Casuística, An. Fac. de med. de Montevideo **5**:202 (May-June) 1920; cited by Rodríguez López. [10d] (*d*) Stajano, C.: La reacción frénica en ginecología: Fisiopatología y mechanismo de la reacción subcostal, ibid. **5**:722 (Nov.-Dec.) 1920; cited by Rodríguez López.[10d]

2. Curtis, A. H.: A Cause of Adhesions in the Right Upper Quadrant, J. A. M. A. **94**:1221-1222 (April 19) 1930.

3. Fitz-Hugh, T., Jr.: Acute Gonococcic Peritonitis of the Right Upper Quadrant in Women, J. A. M. A. **102**:2094-2096 (June 23) 1934.

The purpose of this paper is to report 3 typical cases of gonococcic perihepatitis. The internists and surgeons who saw the patients in consultation were all reluctant to accept the diagnosis. Since the syndrome is apparently not well known, the salient features of the disease will be summarized from the literature and from these cases.

All 3 patients were treated with penicillin and recovered rapidly. Although previous reports of therapy of this particular type of lesion with penicillin have not appeared, the results were to be anticipated in view of repeated demonstrations of its efficacy in other forms of gonococcic infections.

CLINICAL SYNDROME

No cases of gonococcic perihepatitis in men have been reported. The disease occurs chiefly, but not exclusively, in young women, since it is between the ages of 20 and 35 that gonorrhea is most prevalent.

Invariably women in whom the syndrome develops have had an antecedent gonococcic infection, sometimes as far in the past as five years before. At times the peritonitis may have its onset concomitantly with, or may actually seem to precede, pelvic extension of the disease (*las reacciones precoces*).[1c] The initial infection may have been recognized and treated, often inadequately. Incomplete treatment is less common now than formerly, especially when penicillin is used, and reinfections are more frequent. Often it will be impossible to elicit the usual symptoms of gonorrhea because in the female it may assume a latent and entirely asymptomatic form. However, on direct questioning the history will frequently be obtained of menorrhagia or dysmenorrhea, burning on urination, vaginal discharge or vague pain in the lower part of the abdomen during the few days or weeks preceding occurrence of frank symptoms of peritonitis.

The onset is usually dramatic. There is the sudden occurrence of excruciating sharp pain in the upper part of the abdomen, usually on the right side, most intense anteriorly under the rib margins and often referred to the top of the corresponding shoulder. It is of the "pleuritic" type, exaggerated by deep breathing, coughing or laughing and by movements of the trunk, such as bending and walking. The pain may be on the left side or bilateral at the onset [4] and may alternately afflict one side and then the other (*la bascula diafragmatica pelviana*).[1] It may be referred to the inside of the arm as well as to the shoulder.[1] It may be most acute posteriorly, in the lumbar or costovertebral region,[5] or laterally, over the lower ribs. Hiccup may be troublesome. Nausea

4. Claudian, I., and Florian, I.: Le syndrome abdominal supérieur et pleurodiaphragmatique aigu au cours des annexites gonococciques, Ann. de méd. **43**: 62-72 (Jan.) 1938. (*b*) Footnote 1.

5. Hinton, J. W.: Hepatodiaphragmatic Adhesions as a Cause of Upper Abdominal Pain, J. A. M. A. **95**:1744-1745 (Dec. 6) 1930.

is of frequent occurrence, but vomiting follows less often. When symptoms are present in the lower part of the abdomen, they are usually worse on the side of the phrenic reaction, but their intensity is such that they are usually overshadowed by the more acute process in the upper part of the abdomen. Chills, fever, sweats and headache may be present.

It has been repeatedly recognized that trauma to inflamed pelvic organs, in the form of surgical procedures,[1d] gynecologic examination, intercourse or douching, may precipitate the development of this complication. One of the most frequently observed types of reaction in the experience of Stajano [1d] was the postoperative variety. Patients in whom pelvic operations were undertaken before the inflammatory processes had completely subsided and whose natural barriers to the spread of infection beyond the pelvis were ruptured often experienced the phrenic reaction ten to twelve hours postoperatively. Stajano described a patient who had a bilateral phrenic reaction, who was operated on and who underwent a unilateral postoperative reaction; the course of the latter type of complication differed in no way from that of the former.

The physical examination discloses an acutely ill but not prostrated patient. The temperature is usually somewhat elevated, although rarely above 102 F. unless there are additional complications present. There is pronounced tenderness and muscular spasm at the site of greatest intensity of pain, usually in the right upper abdominal quadrant, indicating an underlying peritoneal inflammatory process. As further evidence of this, occasionally a friction rub [6] is heard at the anterior costal margin, which has been described as similar to the "crunching of new snow." [6a] The suspicion of preceding gonorrhea aroused by the finding of slight or moderate tenderness in the lower part of the abdomen is confirmed when other evidences of gonococcic infection—inflammation of Skene's glands or of the glands of Bartholin, urethritis, cervicitis or salpingitis—are discovered.

Slight dulness to percussion at the bases of the lungs posteriorly has often been noted, and small pleural effusions,[4] confirmed by aspiration of small quantities of fluid, occur not uncommonly. Slight or moderate tenderness over the costovertebral angle is not unusual.

Other stigmas of gonococcic infection, such as arthritis, tenosynovitis (case 2) or keratosis blennorrhagica, may be present.

6. (*a*) Fitz-Hugh, T., Jr.: Acute Gonococcic Perihepatitis: A New Syndrome of Right Upper Quadrant Abdominal Pain in Young Women, Rev. Gastroenterol. **3**:125-131 (June) 1936. (*b*) Hahn, T. F.: Gonococcal Peritonitis of the Upper Right Quadrant, J. Florida M. A. **25**:73-75 (Aug.) 1938. Footnote 4. Fitz-Hugh.[3]

Culture of the cervical or urethral secretions under proper conditions invariably yields gonococci. This observation is often not confirmed by examination of stained smears, no matter how painstakingly carried out. Leukocytosis is the rule, although the total count is usually not elevated above 15,000 white cells per cubic millimeter of blood; complications may cause it to be increased above this figure. The gonococcus complement fixation test, carried out on the blood, gives positive results in a variable percentage of cases, from 33 per cent [3] to 100 per cent; [7] hence, it is of diagnostic value only when the result is positive. Fluid aspirated from the pleural cavity is sterile and may vary widely in content of cells.[4a] Especially in patients in whom there occurs perihepatitis, a very slight, transient elevation of bilirubin content of the blood may be found during the height of the process (case 2). A slightly icteric tinge has been noted [6a] uncommonly. Duodenal drainages were performed on 18 patients in one series,[7] with uniformly negative results.

Roentgenologic visualization of the gallbladder by means of radiopaque dye reveals a normally functioning organ, without stones, in nearly every instance.[7] However, especially if the procedure is carried out when the inflammatory process is still acute, a nonfilling gallbladder may occasionally be found, as in Fitz-Hugh's [3] first case. This is not surprising in view of the dense pericholecystic adhesions reported in some instances,[7] which could easily interfere with normal vesical function at an early stage in the course of the inflammation.

The roentgenogram of the chest is usually normal except for some elevation of the diaphragm on the affected side. In 1 case, paresis of the diaphragm on one side was seen fluoroscopically by Stajano.[1a] The roentgenogram of the abdomen reveals normal conditions, no radiopaque stones being visible. There may be an increased amount of gas in the colon.

INCIDENCE

Opinions vary as to the frequency of occurrence of this complication of gonorrhea. Figures are available which differ from a fraction of 1 per cent of all infections, quoted by Brunet,[8] to 10 per cent of all women with "pelvic inflammatory disease," estimated by Maxwell (quoted by Redewill).[9] A survey of the published material on the

7. Boller, R., and Makrycostas, K.: Die chronische Pericholecystitis bei gonorrhoischen Adnexerkrankungen und ihre Behandlung, Klin. Wchnschr. **13**: 1180-1183 (Aug. 18) 1934.

8. Brunet, W. M.: Acute Gonococcal Perihepatitis, with Report of Five Cases, Am. J. Obst. & Gynec. **39**:481-485 (March) 1940.

9. Redewill, F. H.: Acute Gonococcic Perihepatitis: Abdominal Pain in the Upper Right Quadrant in Young Women, Urol. & Cutan. Rev. **41**:685-692 (Oct.) 1937.

subject[10] shows that descriptions of 129 cases have been reported. There is general agreement that this relatively small figure of total reported cases imparts a false impression of the rarity of the syndrome and that it is much commoner than generally believed. This is undoubtedly true, since many cases are diagnosed incorrectly while others escape attention because of the commonly transitory nature of the pain. Peritonitis of the upper part of the abdomen is a not uncommon sequel to gonococcic salpingitis.

PATHOLOGY AND PATHOGENESIS

Although gonococci have not actually been cultured from material taken directly from the subphrenic space at operation, there can be little doubt that they are present. Thus, in Fitz-Hugh's[8] case, typical gram-negative intracellular diplococci were seen in smears of the pus draining from the wound. Mauro[10g] cultured the organisms likewise from the secretions draining through the wound in the upper part of the abdomen.

That the subphrenic process is in the acute stage a true infective peritonitis, not "a mere congestion of the phrenic serosa,"[1a,d] a sort of "sympathetic" reaction to pelvic peritonitis, as Stajano implied, has been demonstrated by Fitz-Hugh, Mauro, Curtis and others. Fitz-Hugh,[8] whose patient was operated on after a ten day period during which her symptoms subsided, noted at laparotomy that a "localized fairly dry peritonitis involved the anterior surface and edge of the liver and the adjacent peritoneal surface of the diaphragm and the anterior abdominal wall. The peritoneum in these areas was injected and had the appearance of salt sprinkled on a moist surface." In Mauro's[10g] case, at operation also, "the surface of the liver was covered with deposits of fibrin of considerable size." Symptoms were of approximately twenty-four hours' duration. Presumably, this acute inflammatory reaction subsides in a few weeks and leaves the "violin string" adhesions in the same location, either between the liver and diaphragm or anterior wall of the abdomen[2] or surrounding the gallbladder.[7] This residue of

10. (*a*) Curtis, A. H.: Adhesions of the Anterior Surface of the Liver, J. A. M. A. **99**:2010-2012 (Dec. 10) 1932. (*b*) Bearse, C.: Gonorrheal Salpingitis and Perihepatic Adhesions, ibid. **97**:1385 (Nov. 7) 1931. (*c*) Hertz, C. S.: Acute Gonococcic Perihepatitis, Proc. Staff Meet., Mayo Clin. **13**:577-581 (Sept. 14) 1938. (*d*) Rodríguez López, M. B.: El sindrome subcostal y de reacción frénica del profesor doctor Carlos Stajano en las anexitis gonocóccicas, Arch. urug. de med., cir. y especialid. **16**:313-319 (April) 1940. (*e*) Hudgins, A. P.: Acute Gonococcic Perihepatitis, West Virginia M. J. **37**:77-79 (Feb.) 1941. (*f*) Steinberg, B.: Infections of the Peritoneum, New York, Paul B. Hoeber, Inc., 1944, pp. 231-241. (*g*) Curtis.[2] Hinton.[5] Footnote 6. Boller and Makrycostas.[7] Brunet.[8] Redewill.[9] Mauro, E.: Le syndrome abdominal droit supérieur au cours des annexites gonococciques (syndrome de Fitz-Hugh), Presse méd. **46**:1919-1921 (Dec. 28) 1938.

adhesions may persist indefinitely. Recently, an 80 year old woman who died after a pulmonary infection was seen at autopsy to have typical subphrenic adhesions along with healed salpingitis and evidences of healed pelvic peritonitis. One can only estimate their duration, but it is probable that they had remained twenty or more years.

There appears to be almost no tendency toward abscess formation in the subdiaphragmatic space following its invasion by the gonococcus. The subphrenic abscess reported by Scott [11] is a distinct rarity. In this case, too, the diagnosis was made by smear, and cultures of the pus from the abscess were sterile. However, similar organisms were also seen in the cervical smear. Of a series of 3,608 collected and personal cases of subphrenic abscesses (Ochsner and De Bakey [12]) in only 54 (1.5 per cent) could the process be said to have its origin in the female genitalia. It was not possible to say how many of these were of gonococcic origin. Thus, the course of the disease is different from that of infections of the same region due to colon bacilli, streptococci and Staphylococcus aureus, the major causes of subphrenic abscesses. However, even when the latter organisms are present, abscess formation does not occur in every case of subphrenic infection. Ochsner and De Bakey [12] said: "In our experience approximately 70 per cent of subphrenic infections which are diagnosed from the clinical manifestations subside without proceeding to suppuration." Neuhof,[13] Lee [14] and Clendening [15] described cases in which spontaneous recovery was the conspicuous feature.

From study of the biopsy material in his first case, Fitz-Hugh [6a] was able to state that "the inflammation of the liver capsule may extend into the outer zone of the liver parenchyma which, in one of my sections from case 1, showed some small islands of regenerating liver cells surrounded by strands of inflammatory connective tissue dipping in from the capsule." It may be, then, that the mild, transient and usually subclinical icteric states occasionally seen (case 2) can be accounted for by actual peripheral hepatitis.

Much has been written about the route of extension of the infection from the pelvis to the subphrenic spaces, whether via the paracolic

11. Scott, G. D.: Subdiaphragmatic Gonorrheal Abscess, J. A. M. A. **96:** 1681-1682 (May 16) 1931.

12. Ochsner, A., and De Bakey, M.: Subphrenic Abscess: Collective Review and an Analysis of 3,608 Collected and Personal Cases, Internat. Abstr. Surg. **66:**426-438 (May) 1938.

13. Neuhof, H.: Non-Suppurative Subphrenic Peritonitis Complicating Appendicitis, Surg., Gynec. & Obst. **14:**231-246 (March) 1912.

14. Lee, R. I.: Subdiaphragmatic Inflammation with a Syndrome of Physical Signs and Spontaneous Recovery Without Suppuration, J. A. M. A. **64:**1307-1310 (April 17) 1915.

15. Clendening, L.: Subphrenic Infection: Cases Illustrative of the Different Forms of This Condition, M. Clin. North America **7:**1147-1167 (Jan.) 1924.

gutter or through the retroperitoneal lymphatics. While there is not enough evidence to settle the question—if, indeed, there is only one method in all cases—it may be said that it is the rule to encounter tenderness in the middle part of the abdomen laterally, indicating inflammation of the peritoneum between the pelvis and diaphragm. Thus, Miller,[16] on several occasions when he operated before complete subsidence of the infectious process, noted that "considerable peritoneal fluid was present and granular exudate, agglutinating several coils of the intestine, was found as high up as the level of the umbilicus." At least in some instances, then, there is direct extension rather than metastasis.

DIAGNOSIS

When one is presented with the clinical picture previously described, especially in a young woman, the diagnosis can be made with a high degree of certainty by merely establishing the presence of gonococci in the urethra or cervix. That this decision should be made on the basis of culture, and not of smears alone, cannot be too strongly emphasized. Thus, in 2 of the 3 cases reported herein smears were repeatedly negative or inconclusive although the organisms were easily cultured in large numbers. It should be reiterated that gonorrhea in women is often relatively asymptomatic, hence extremely difficult to detect clinically. The most reliable method of diagnosis is by culture of the causative organism.

It has been the experience of workers in the bacteriology laboratory where my work is done that the growth of gonococci has not been difficult on beef heart infusion tryptose agar with 10 per cent defibrinated sheep blood employed routinely for blood agar plates. For use in isolating the organism from clinical material (pus) the p_H should be adjusted to between 7.6 and 7.8 rather than 7.2, the reaction commonly employed in growth of stock cultures. The plates should be incubated in a candle jar or other device for attaining approximately 2 per cent concentration of carbon dioxide in the surrounding atmosphere.

DIFFERENTIAL DIAGNOSIS

The most frequently encountered diagnostic problem is differentiation of gonococcic peritonitis from acute cholecystitis. In the acute stage there may be a nonfilling gallbladder, which further confuses the picture. When the inflammation assumes the form of pericholecystitis, differentiation may be impossible. It should be remembered that gallstones are uncommon before the age of 30, especially in women who are not fat, and that pain is not often referred to the top of the shoulder and the root of the neck via the phrenic nerve unless the inflammation is subphrenic rather than subhepatic. Other abdominal conditions from

16. Miller, H., in discussion on Curtis.[10a]

which this disease must be differentiated include ruptured peptic ulcer, appendicitis with subphrenic abscess and other forms of peritonitis. If the pain is greatest posteriorly, as in Hinton's [5] case, pyelitis, nephrolithiasis or perinephric abscess must be considered. In the chest pneumonia of the lower lobe of the lung and pleurisy due to other causes may have to be ruled out. Herpes zoster and epidemic pleurodynia are other possibilities.

An accurate diagnosis is important, especially in ruling out those diseases requiring surgical intervention, for not only is such interference unnecessary but it may actually be harmful. Presence of other complications of gonococcic infection, such as arthritis or tenosynovitis, may simplify the process of differentiation. A past history of any venereal disease is obviously an important indication of the possibilities of multiple infections, of which gonorrhea may be one.

COURSE AND PROGNOSIS; TREATMENT

There have been no deaths reported as resulting from this type of gonococcic peritonitis. The usual course when it is untreated is slow subsidence of the acute pain to a dull ache which gradually disappears, the whole process requiring from one to four weeks. One of the astonishing features is the rapid decline of symptoms and the commonly transitory nature of the acute process without any treatment. However, in such instances recurrences are frequent. After the inflammation has abated and the adhesions have formed there is no reason to believe that pain will persist unless, of course, as often happens, there is a recurrence.

The therapy which has been employed in the past has been that most popular at the time the cases were described. Thus, gonococcus vaccine, hyperpyrexia and the various sulfonamide compounds have been used with varying success. At the present time penicillin is the drug of choice; with doses of 20,000 units administered every three hours intramuscularly, there is almost complete relief of symptoms after twenty-four hours of treatment. Opinions vary as to the amount of the drug necessary for cure of gonorrhea, and figures ranging from 75,000 to 300,000 units [17] have been given. It is probable that forty-eight hours

17. (*a*) Cohn, A.; Studdiford, W. E., and Grunstein, I.: Penicillin Treatment of Sulfonamide Resistant Gonococcic Infections in Female Patients, J. A. M. A. **124**:1124-1125 (April 15) 1944. (*b*) Lapenta, R. G.; Weckstein, A. M., and Sarnoff, H.: The Inadequacy of a Standardized Dosage of Penicillin in the Treatment of Gonococcic Urethritis, ibid. **128**:168-170 (May 19) 1945. (*c*) Harford, C. G.; Martin, S. P.; Hageman, P. O., and Wood, W. B., Jr.: Treatment of Staphylococcic, Pneumococcic, Gonococcic and Other Infections with Penicillin, ibid. **127**:325-329 (Feb. 10) 1945. (*d*) Greenblatt, R. B., and Street, A. R.: Penicillin for the Treatment of Chemoresistant Gonorrhea in the Female, ibid. **126**:161-163 (Sept. 16) 1944.

of therapy (320,000 units) is more than adequate for cure of the disease in the form under discussion. In speed and certainty of cure penicillin far surpasses any other agent ever used in treating gonorrhea.

REPORT OF CASES

CASE 1.—M. H., a 27 year old Negro woman who was living apart from her husband, was admitted to the Evans Memorial Hospital on Oct. 14, 1944, complaining of severe pain in the right upper abdominal quadrant, aggravated by respirations and of twenty-four hours' duration.

Past History.—Three years before the present illness, in November and December 1941, she had had pain, swelling and redness involving the left ankle, right foot and right elbow and, later, the dorsum of the right hand as well as the left shoulder. On Jan. 5, 1942, there was residual swelling over the left subacromial region, with tenderness and pain on motion of the left shoulder. There had been no symptoms indicative of gonococcic infection except a vaginal discharge. Gram-negative, intracellular diplococci were seen in the smear of materials from the cervix uteri. The sedimentation rate was 50.5 mm. per hour. The subacromial bursitis gradually improved following irrigation of the bursa and physical therapy. During the following eleven months she visited the clinic sporadically; in this period gonococci were cultured from the cervix several times. She was treated with local applications and with one course of sulfathiazole and was discharged as cured on Nov. 30, 1942, after three cultures and smears of cervical materials were negative for gonococci.

Present Illness.—Three months before entry she had fever, severe suprapubic pain, dysuria and a yellow vaginal discharge. These symptoms, except for a persistent discharge, subsided promptly after treatment with hot douches and rest in bed. Two weeks before admission (on the third day of her menstrual period) and one week after sexual exposure, the severe pain in the lower part of the abdomen returned, accompanied with malaise and anorexia. The symptoms continued until entry.

On the morning before entry the patient was awakened by a severe constant nonradiating pain in the right upper part of the abdomen, aggravated by deep breathing, coughing and motion of the trunk. No pains in the shoulders or back, chills, fever, nausea, vomiting or diarrhea was noted. There had been no previous similar attack. There had been no indigestion, intolerance to fatty foods or jaundice.

Physical Examination.—The patient was a well developed and well nourished young woman in moderate pain. The rectal temperature was 99.6 F. There was diminution of excursion of the right side of the diaphragm and slight dulness at the base of the right lung, but no other abnormalities of the lungs. The abdomen was slightly distended. There were pronounced tenderness and spasm over the right upper part of the abdomen and slight tenderness over the right lower quadrant and right lumbar region. The edge of the liver descended 2 cm. below the right costal margin on deep inspiration, which aggravated the pain. The spleen was not palpable. There was a profuse thick, creamy vaginal discharge. The uterine cervix was bilaterally lacerated, with extensive erosion. There were bilateral induration and thickening of the adnexa, more pronounced on the right. Motion of the cervix produced exquisite pain.

Laboratory Data.—Two Hinton tests of the blood elicited negative reactions. Results of several urinalyses were entirely normal. The white blood cell count on admission to the hospital was 11,300, with 87 per cent polymorphonuclear

leukocytes, and ranged between 10,000 and 13,000 until completion of treatment, when it dropped to normal. The icterus index and serum bilirubin content were normal. A roentgenogram of the chest showed a bilateral increase in hilar shadows, more pronounced on the right. A roentgenogram of the abdomen revealed only a moderately increased amount of gas in the colon. There were no radiopaque calculi. After completion of treatment an intravenous cholecystogram revealed entirely normal conditions. In smears of material from the urethra and cervix no intracellular gram-negative diplococci could be found. However, a heavy growth of gonococci was obtained from culture of the cervical secretions.

Course in the Hospital.—Because of lack of immediate confirmation of the diagnosis surgical consultation was obtained. The attending surgeon's diagnosis was acute cholecytitis, for which a prompt operation was strongly considered. However, symptomatic and conservative treatment was instituted until the report of the cultures was received. On the fourth day of hospitalization therapy with penicillin was begun, in doses of 20,000 units every three hours, intramuscularly. A total of 380,000 units was given. Within twenty-four hours after the institution of specific therapy all the abdominal pain had disappeared, and the course thereafter was one of rapid recovery. The rectal temperature, which had ranged between 98 and 101 F., rapidly subsided to normal after the beginning of treatment. The patient was discharged eleven days after admission. Cervical and urethral cultures made two and three weeks after discharge were negative for gonococci.

CASE 2.—M. G., a 30 year old white divorced waitress in a waterfront cafe, was admitted to the hospital on June 4, 1945, with a painful swelling of her right hand of three days' duration and pain over the entire right side of the abdomen and the top of the right shoulder of twenty-four hours' duration.

Past History.—At 15 years of age the patient had had septicemia and osteomyelitis, which had resulted in the formation of draining sinuses of the left humerus, left twelfth rib and lower end of the right tibia. After surgical drainage of these foci and removal of the rib she made a satisfactory recovery. Thirteen months before admission a diagnosis of gonorrhea was made on the basis of positive cultures at another hospital, to which she had been referred as a contact of a known patient. She was asymptomatic at that time. The serologic reaction of the blood was positive for syphilis, although she stated that she had not had symptoms of early infection. She was treated for two weeks with a sulfonamide compound and was told that the cultures were negative at the end of this period. During the next seven months several cultures of cervical and urethral materials were negative for gonococci. During the six months prior to admission she had received sporadic antisyphilitic treatment, consisting of six intramuscular injections of bismuth subsalicylate.

The patient's alcoholic intake was immoderate during the preceding seventeen years; it was particularly so during the last three, when she was intoxicated almost daily. She had separated from her husband four years earlier, after four years of marriage. She had had one abortion. Her husband was known to have had gonorrhea while she was living with him.

Present Illness.—Three days prior to admission the dorsum of her right hand was first noted to be painful. During the following forty-eight hours it became increasingly swollen, hot and red. One day before admission she was awakened by severe pain both in the right upper and lower quadrants of the abdomen and over the top of the right shoulder. The pain in the upper part of the abdomen did not radiate; it was constant, although made worse by coughing and deep breathing.

The pain on the top of the right shoulder radiated into the neck toward the ear; it was also exaggerated by coughing and deep inspiration but not by movement of the shoulder joint. On the morning of admission there was a slight ache in the left wrist but no other signs of inflammation. There were no chills, sweats or fever.

The menstrual flow was irregular during the three months before her illness, although it had previously been normal. Her last menstrual period was of fifteen days' duration, and it had ceased the day before the onset of her symptoms. The day before admission vaginal bleeding began again. She stated that she had never had leukorrhea, dysuria, urinary frequency or pyuria. The last sexual exposure had taken place four days before her symptoms began. There had been no other episodes of similar nature; she had never been jaundiced, nor had there been indigestion, intolerance to fatty foods or flatulence.

Physical Examination.—The patient was obese and acutely ill. The dorsum of the right hand was tender, hot, red and swollen, pitting on moderate pressure. Passive motion of the fingers was extremely painful, although motion of the wrist was unaffected. There was slight pain on movement of the left wrist, which appeared otherwise normal. The right shoulder joint was apparently normal; there was no tenderness, and motion in all directions was painless. The heart and lungs were normal. Diaphragmatic excursion was limited on the right because of pain. The abdomen was protuberant. There were decided spasm and tenderness over the entire right side of the abdomen. Pressure over the right upper quadrant accentuated the pain in the top of the right shoulder. There was a vague mass in the right upper quadrant which was considered by some observers to be an enlarged liver, although the lower edge was never palpated. No other masses were felt, and peristalsis was normal. Slight tenderness of the right costovertebral angle was noted. Pelvic examination showed a moderate amount of cervical erosion, with a transverse laceration. Movement of the cervix and palpation of both adnexa were exquisitely painful. No masses were felt. The urethra was normal. Skene's and Bartholin's glands were not palpable. There were several pulsating "spider" angiomas on the skin of the upper half of the body and many dilated venules on the face.

Laboratory Data.—Reaction of the blood to the Hinton test for syphilis was positive. Cultures of material from urethra and cervix were positive for gonococci, although smears were repeatedly found to be negative. The results of repeated urinalyses were normal. The white blood cell count was 23,400 with 76 per cent polymorphonuclear leukocytes on admission and gradually fell to 11,800 on discharge. The result of a complement fixation test for gonorrhea (Schwartz-McNeil) on the blood was positive. The total serum bilirubin was 1.14 mg. per hundred cubic centimeters, with 0.72 mg. per hundred cubic centimeters of direct reacting bilirubin on admission. There were 0.72 mg. and 0.18 mg. respectively, at the end of treatment. The cephalin flocculation reaction was negative. The sulfobromophthalein sodium excretion was within normal limits, as determined by the fractional method. A roentgenogram of the chest showed no abnormality except for elevation of the left side of the diaphragm.

Course in the Hospital.—As soon as the report of the cultures was known treatment with penicillin was started. The patient received 20,000 units intramuscularly every three hours. Within twenty-four hours after the institution of therapy, the temperature, which had previously ranged between 98 and 102 F. rectally, had returned to normal, and there was great improvement in her symptoms. After forty-eight hours of treatment there remained only slight residual soreness

in the right lower abdominal quadrant and moderate painless swelling of the dorsum of the right hand. Cultures of material from the urethra and cervix at this time were negative. Because she had not visited the syphilis clinic regularly, the patient was given a total of 1,200,000 units of penicillin in order to complete treatment of her latent syphilis. She left the hospital the fourteenth day after admission, entirely asymptomatic. Cultures after forty-eight hours of treatment and one and three days after the completion of treatment were negative.

CASE 3.—B. B., a 23 year old married Negro woman, was admitted to the surgical service of the Massachusetts Memorial Hospitals on Jan. 3, 1945, complaining of severe pain in the epigastrium of four hours' duration.

Past History.—In 1941 a diagnosis of early latent syphilis had been made. Since that time she had received antisyphilitic treatment consisting of a total of thirty-one injections of bismuthsubsalicylate in oil and thirty injections of various arsenical preparations.

Since 1940 she had had four pregnancies, the first an abortion at 4½ months. The last child, born three months prior to this entry to the hospital, was apparently normal at birth but died at 7 weeks of age of unknown cause. There were two healthy children.

Present Illness.—During the six weeks prior to admission the patient had noticed a profuse purulent vaginal discharge and slight dysuria. Waves of nausea and anorexia occurred during the two days preceding entrance. On the night before admission she had a drenching sweat. She was awakened on the morning of admission by a severe pain in the upper part of the abdomen; the point of maximal intensity was in the midepigastrium. The pain was sharp and nonradiating and was made worse by coughing, talking or deep breathing. There was no vomiting. No shoulder ache or backache occurred. No increase in severity was produced by ingestion of food. There had been no similar episodes previously. No symptoms suggestive of disease of the gallbladder could be elicited.

Physical Examination.—The patient was thin, apprehensive and in evident pain. The heart was normal except for a rough grade II late systolic murmur, loudest over the second intercostal space at the sternal border on the left side. The murmur was not transmitted to the neck. The lungs were normal. In the abdomen pronounced tenderness and accompanying spasm of the musculature of the right upper quadrant and epigastrium were present. The liver was not palpable. Peristalsis was normal. Slight tenderness of the right costovertebral angle was found. Pelvic examination disclosed a thick purulent vaginal discharge, with erosion and laceration of the cervix. Only slight tenderness was elicited on palpation of either of the adnexa, and there were no masses.

Laboratory Data.—The Hinton test of the blood for syphilis elicited a positive reaction. The culture of cervical material was positive for gonococci, but the culture of urethral material was negative. The urine was normal except for a small amount of ketones. The white blood cell count was 15,800 with 92 per cent polymorphonuclear leukocytes on admission.

Course in the Hospital.—Treatment was immediately started with intramuscular injections of 15,000 units of penicillin, every three hours for a total of 195,000 units. The temperature, which was 102 F. on admission, had dropped to normal twelve hours later. At this time the patient was entirely asymptomatic. She left the hospital on the third day and failed to report for follow-up studies.

SUMMARY AND CONCLUSIONS

Three cases of gonococcic perihepatitis treated with penicillin are described in detail.

The clinical and pathologic picture of gonococcic peritonitis of the upper part of the abdomen is summarized as it has been developed since Stajano's original description.

From the data, the following conclusions may be drawn:

1. The disease occurs more commonly than is generally believed. It should be considered in the differential diagnosis for every young woman in whom an acute pain develops in the upper part of the abdomen, especially on the right side. It is most commonly misdiagnosed as acute cholecystitis.

2. Gonorrhea in the female is often latent and relatively asymptomatic; hence, it is difficult to diagnose clinically. The unreliability of smears is stressed; culture of the gonococcus is the only reliable method of diagnosis in many cases and should be carried out routinely.

3. The importance of correct diagnosis is obvious, since surgical intervention not only is unnecessary but may be actually harmful. Gonococcic peritonitis is easily and successfully treated with penicillin.

MYELOFIBROSIS, SPLENOMEGALY AND MEGAKARYOCYTIC MYELOSIS

Report of a Case

LIEUTENANT HOWARD W. CRAIL (MC), U.S.N.R.

FROM time to time cases have been reported in the literature in which there were splenomegaly and an unusual white blood cell count, which do not fit into any recognized pathologic category. Such cases are reported as: "Chronic nonleukemic myelosis" [1]; "myelofibrosis associated with a leukemoid blood picture" [2]; "osteosclerosis with extensive extramedullary hematopoiesis and a leukemoid blood picture" [3]; "marrow sclerosis associated with massive myeloid splenomegaly" [4]; "splenomegaly with myeloid transformation" [5]; "megakaryocytic myelosis with osteosclerosis," [6] and "aleukemic myelosis with osteosclerosis." [7] The similarity between these cases and the one reported

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From the Department of Pathology, Naval Medical School, National Naval Medical Center, Bethesda, Md.

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1. (*a*) Hickling, R. A.: Chronic Non-Leukemic Myelosis, Quart. J. Med. **6**:253, 1937. (*b*) Carpenter, G., and Flory, C. M.: Chronic Nonleukemic Myelosis: Report of a Case with Megakaryocytic Myeloid Splenomegaly, Leukoerythroblastic Anemia, Generalized Osteosclerosis and Myelofibrosis, Arch. Int. Med. **67**:489 (March) 1941.

2. Mettier, S. R., and Rusk, G. Y.: Fibrosis of Bone Marrow (Myelofibrosis) Associated with Leukemoid Blood Picture: Report of Two Cases, Am. J. Path. **13**:377, 1937.

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4. Taylor, H. E., and Smith, R. P.: Marrow Sclerosis Associated with Massive Myeloid Splenomegaly, Arch. Path. **31**:803 (June) 1941.

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here is striking and suggests the possibility of a disease entity which is infrequent enough to elude early recognition.

All of these cases in which there was splenomegaly have been characterized by megakaryocytes in the spleen, liver, lung, lymph nodes, peripheral blood and elsewhere with an accompanying disturbance in the number and type of circulating platelets. The circulating white blood cells, regardless of the total count, have shown myeloblastic forms. All of them have shown, either on roentgenologic studies or on autopsy, sclerosis or fibrosis of the bone marrow. The hemopoietic organs have shown not true leukemic infiltrations and proliferations but foci of extramedullary hemopoiesis. In addition, a strikingly large percentage have shown focal lesions in the lungs, liver or kidneys, variously described as infarcts, tubercles, abscesses or necrosis. In some of these cases acid-fast organisms have been demonstrated, although in a majority of the cases reported no studies have been carried out to determine the presence of such organisms.

In the present paper an additional case is reported, and its major features are correlated with the findings concerning similar cases in the literature.

REPORT OF A CASE

Clinical History.—The patient, a 36 year old white woman, was apparently well and healthy after the normal delivery of a 6 pound, 9 ounce (2,977 Gm.) baby girl on Oct. 11, 1944. Two days post partum an enlarged spleen was found. She was sent home from the hospital fourteen days after delivery but required continued medical care. A diagnosis of Banti's disease was made. She was readmitted to the hospital, and a splenectomy was done on Nov. 14, 1944. The pathologic report on the spleen indicated Hodgkin's disease. She left the hospital on Nov. 25, 1944, to convalesce under the care of relatives until March 1945, and during this time she gained approximately 35 pounds (16 Kg.). She then returned home and resumed care of her baby. In May 1945 her menstrual period came at the regular time but lasted twelve days, and she passed numerous large clots. At this time she caught a cold, and her temperature rose as high as 103 F. Her physician advised her to get more rest. Her general health failed to improve. She complained of weakness, night sweats, occasional headaches, a nonproductive cough and pleuritic pains localized at the level of the eighth thoracic vertebra. She was hospitalized for study on June 23, 1945. During this hospitalization she lost weight, and her stools became tarry.

Past History.—An appendectomy was performed in 1932. She had the usual diseases of childhood and had pneumonia in 1934. Her previous hospital record showed a single positive reaction to a Kahn test taken Oct. 15, 1944 (the reaction of blood from the cord at the time of delivery was reported negative), and she was considered syphilitic, being treated in 1943 and early 1944.

Family History.—Her mother died at the age of 42 from thyroid disease, her father died at the age of 79 from arteriosclerosis. One sister died of tuberculosis. Four other children in the family are living and well.

Physical Examination.—The temperature was 100.2 F., the pulse rate 100 and the respiration rate 24. The conjunctivas were pale. The lungs were clear, and

the examination of the heart revealed a soft systolic murmur at the base. There was a large, smooth, firm, mobile, nontender mass in the right upper and lower quadrants extending down to the rim of the pelvis. This was interpreted as an enlarged liver. The mass did not extend to the left side of the abdomen, which showed only the scar of the former splenectomy. The neurologic examination revealed no significant abnormalities. A moderate generalized nontender lymphadenopathy and a nonproductive cough were noted.

Special Studies.—The hemacytologic studies (table 1) revealed a progressive anemia with achromia, polychromatophilia, poikilocytosis and anisocytosis. The elevated white blood cell count and the presence of abnormal leukocytes were not apparent until the third admission. The most unusual findings were made during her fourth admission. The leukocyte count reached 115,000, then gradually declined to 34,000 with immature myeloid cells predominating. The platelet count extended well above 500,000, the platelets being too many to count in most instances. Many megakaryocytes in all stages of development and giant platelets were found in the peripheral blood smears (fig. 1).

The sternal marrow aspiration (table 2) was unusual in that the blood was under considerable pressure and clotted spontaneously in the syringe, so that the routine hematocrit determination was not done and good smears were difficult to obtain. The young myeloid cells predominated with a great increase in the number of megakarocytes, and it was concluded that acute myeloid leukemia with pronounced megakaryocytic hyperplasia was indicated.

The serologic reports included two positive reactions to the Kahn test obtained prior to antisyphilitic therapy initiated in 1943, a single positive reaction to the Kahn test recorded during her first hospitalization in 1944, a negative reaction to the Kahn test of blood taken from the cord on delivery of her baby and two negative reactions to the Kahn test during the patient's last hospitalization. Studies of the spinal fluid were not done.

Studies of blood chemistry revealed a fasting glucose level of 80 mg., a cholesterol level of 236 mg. and a nonprotein nitrogen level of 33.5 mg. per hundred cubic centimeters, the latter being 55 mg. a few hours prior to death.

The results of urinalysis remained fairly constant, with an acid reaction, a specific gravity of 1.020, an albumin level of 35 mg. per hundred cubic centimeters and 7 to 9 leukocytes per high power field.

Additional laboratory studies revealed the following results: sedimentation rate, 6 mm. in five minutes and 32 mm. in sixty minutes; bleeding time, three and one-half minutes; clotting time, two minutes; coagulation time one minute; prothrombin time ranging between 57 and 92.3 per cent of normal, and blood type Rh negative.

Roentgenologic studies were not unusual prior to July 1945, at which time a pronounced enlargement of the liver was reported. A roentgenogram of the chest taken in August 1945 demonstrated significant widening of the upper mediastinum with some general cardiac enlargement. The left side of the diaphragm was completely obscured, and there was increased density of a moderate degree over both lower lung fields suggestive of minimal pleural effusion. A roentgenogram of the chest taken in September 1945, a few days prior to death, showed a significant diffuse flocculent increase in density involving both lung fields, most pronounced at the bases. However, the diaphragm leaves were well visualized and the angles clear. This suggested an acute pulmonary edema without pleural effusion.

TABLE 1.—*Blood Counts*

Date	R.B.C., Million	Hgb.	W.B.C.	My.	Juv.	Bands	Seg.	L.	B.	Promy.	Blasts	Stab	Trans.	Norm.	Mono.	Comment
First Admission																
10/19/44	3.8	56%	17,600	..	3	..	59	28	..	..	..	5	..	..	5	Achromia, polyehromatophilia
Second Admission																
11/13/44	3.5	58%	6,700	..	8	..	38	40	..	..	..	12	..	..	2	Anisocytosis, polychromatophilia, achromia
Third Admission																
6/21/45	2.0	31%	97,500	2	..	..	18	20	9	..	..	..	..	..	47	
6/30/45	1.9	30%	60,000	10	..	..	14	22	4	..	..	..	8	31	52	
Fourth Admission (Fig. 1)																
7/ 9/45	2.7	45% 6.5 Gm.	41,750	4	7	2	14	8	6	32	27	..	..	..	..	Platelets: 500,000; retic. 0.5%
7/12/45	2.4	46% 6.75 Gm.	34,350	4	2	5	8	7	5	10	59	There were many megakaryocytes in all stages of development				Platelets; innumerable
8/13/45	3.5	61% 8.7 Gm.	115,500	6	8	4	5	2	2	13	60	..	..	..	.. ..	Platelets: innumerable
9/18/45	1.9	36% 5 Gm.	35,000	8	11	7	4	5	6	22	37	..	..	..	..	Platelets: innumerable

* These blood counts were selected as representative from daily counts during hospitalization.

Electrocardiographic studies resulted in no significant observations.

The basal metabolic rate, measured in July 1945, was + 15 per cent on the first test and + 20 per cent on the second test.

During the patient's last admission the pathologic material from the spleen was reexamined and reported suggestive of myelogenous leukemia.

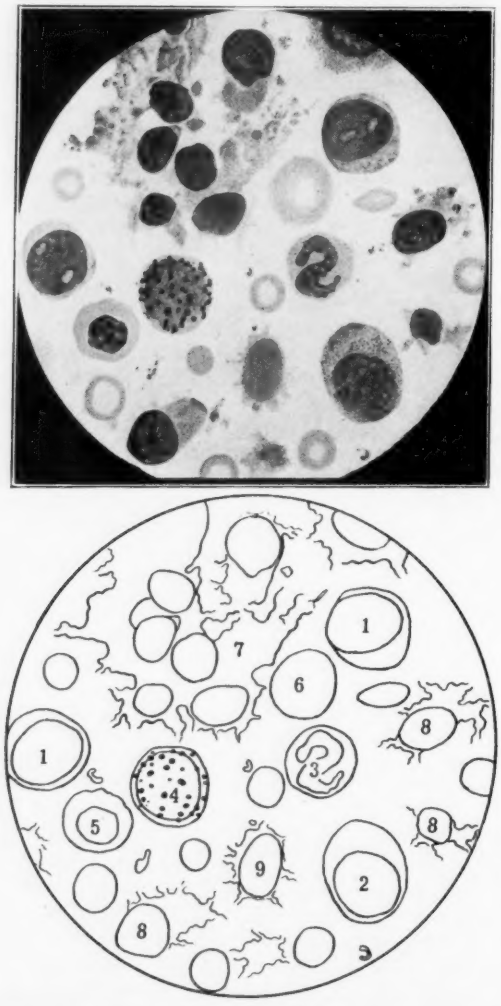

Fig. 1.—A composite drawing from blood smears obtained from the peripheral blood in the case herein reported: *1*, myeloblast; *2*, promyelocyte; *3*, band neutrophil; *4*, basophil; *5*, normoblast; *6*, macrocytic erythrocyte; *7*, megakaryocyte; *8*, detached portions of megakaryocytes, and *9*, giant platelet.

Clinical Course.—The treatment was predominantly symptomatic with repeated blood transfusions of Rh negative blood. She grew progressively worse, becoming extremely emaciated and jaundiced and having increased malaise and discomfort. Her temperature was high because of sepsis, the peaks ranging between 104 F. and 105 F., with terminal evidence of delirium and mental changes. In the last week of her life ascites and jaundice were present. She died on Sept. 21, 1945.

Necropsy.—A necropsy was performed on Sept. 21, 1945.

General: The body was that of an extremely emaciated woman, 36 years of age and weighing approximately 98 pounds (44.5 Kg.). She had a sallow, jaundiced appearance. The right pupil was slightly smaller than the left, and both were dilated. There was an abdominal scar over the lower part of the right rectus muscle and a curved "hocky stick" scar covering the left side of the abdomen. A slight protuberance was noticeable about the umbilicus surrounded by an area of bluish discoloration beneath the skin which extended into the left upper quadrant. There was pitting edema over both ankles. There was a bedsore about 2.5 cm. in diameter in the upper lumbar area. Generalized lymphadenopathy was prominent.

Thoracic Cavity: Both pleural cavities were obliterated by firm adhesions between the visceral and parietal pleurae. There was no free fluid in either pleural cavity. The lungs were removed with difficulty.

Lungs (fig. 2): The left lung weighed 720 Gm. It was subcrepitant, and the surface was studded with numerous small grayish white, firm nodules varying

TABLE 2.—*Bone Marrow*

	July 9, 1945		
Myeloblasts	24.6	Lymphocytes	14.0
Promyelocytes	22.8	Monocytes	0.6
Myelocytes	6.2	Megaloblasts	0.4
Juvenile forms	4.8	Erythroblasts	0.2
Bands	6.6	Normoblasts	55.6
Segmented cells	13.8	Pronormoblasts	1.4
Eosinophils	0.8	Megakaryocytes	Great increase
Basophils	5.8		

in size from 0.1 to 0.5 cm. The larger vessels were patent; the bronchi contained a frothy material, and edema fluid could be expressed on compression of the lung tissue. The cut surface revealed massive studding of the tissue with small white nodules similar to those on the surface of the uncut organ, and free fluid ran from the cut surface. The lobes were equally involved. The right lung weighed 1,090 Gm. and was in all respects similiar to the left lung. The hilar and mediastinal lymph nodes were enlarged and matted together and had a pinkish gray color when opened.

On microscopic study the alveolar septums were thickened, and their capillaries were crowded with red cells, occasional nucleated red cells, early myeloid cells, megakaryocytes and scattered fibrin. Some of the alveoli contained edema fluid; many contained cells of various types including heart failure cells. The bronchial epithelium showed areas of patchy erosion and the bronchi appeared empty. The surrounding connective tissue was edematous and infiltrated with round cells. Scattered throughout the sections were focal areas of infarction with early necrosis and degeneration of the lung tissue and deposition of considerable fibrin. The

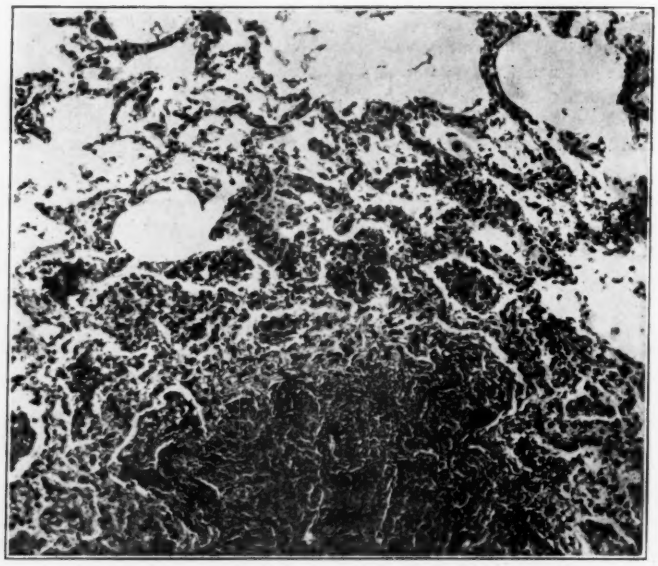

Fig. 2.—Photomicrograph of lung showing an area of focal infarction surrounded by a zone of extramedullary hemopoiesis.

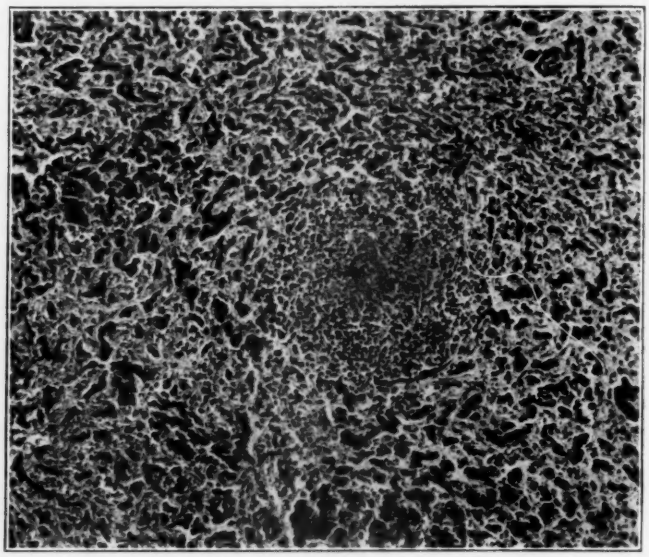

Fig. 3.—Photomicrograph of liver showing miliary tubercle and associated fibrosis.

infarcts were surrounded peripherally by a zone of cells, which include myeloblasts, megaloblasts, normoblasts, megakaryocytes and numerous phagocytes. This surrounding zone contained so many blast forms that it suggested extramedullary hemopoiesis. Epithelioid cells and lymphocytes were not seen. In sections stained by the Ziehl-Neelsen technic great numbers of acid-fast bacilli were found in the infarcted areas, and many were intracellular.

Heart: There was a small plaque on the pericardial surface of the heart over the left ventricle which measured approximately 0.9 cm. in diameter. The coronary ostia were patent. There were numerous subintimal plaques throughout the course of the coronary arteries, but the lumens remained widely patent. The heart valves, the auricles and the ventricles appeared normal.

The sections showed thinning of the myocardial bundles which were widely separated by edema. The coronary arteries showed subintimal thickening with early degenerative changes. An occasional early myeloid cell and phagocyte could be seen in the connective tissue surrounding the vessels.

Aorta: The aorta was normal in appearance, grossly and microscopically.

Abdominal Cavity: Five hundred cubic centimeters of dark, straw-colored fluid was found in the abdominal cavity. There was a small adhesion of the greater omentum to the scar on the lower part of the abdomen and to the stomach and transverse colon in the left upper quadrant. The omentum was almost completely devoid of fat. The peritoneal surfaces, both visceral and parietal, were studded with small grayish white nodules. The spleen and appendix were absent, having been surgically removed.

Liver (fig. 3): The liver weighed 2,670 Gm. Its lower border extended about 3 fingerbreadths below the right costal margin. The edge was broad and rounded. The surface was pale and studded with small grayish white nodules. The gallbladder contained 10 cc. of dark green bile. The cut surface of the liver was pale and slightly congested and showed an extensive peppering of the small grayish white nodules.

Histologic study showed areas of focal necrosis and infarction surrounded by zones of hemopoiesis similar to those seen in the lung. The hepatic cells and cords were small and surrounded by hyalinized connective tissue which obliterated many of the sinuses. The portal triad was similarly infiltrated with connective tissue and round cells. On and beneath the capsule were accumulations of immature erythrocytes and leukocytes. Special stains of these sections showed many acid-fast bacilli in the multiple necrotic zones, and many were intracellular.

Spleen (fig. 4): The spleen was surgically removed and not available for examination. Microscopic slides revealed considerable necrosis and scattered pigment. Numerous large myeloblasts and megaloblasts and frequent megakaryocytes were seen. The lymph follicles were few, and lymphocytes were sparsely distributed. The sinuses contained many myeloblasts, a few lymphocytes, red blood cells and much debris. An occasional multinucleate cell might be seen. Acid-fast stains of the tissue available failed to demonstrate the presence of organisms.

Gastrointestinal Tract: The gastrointestinal tract revealed nothing remarkable except for the nodules previously described on the peritoneal surface. The sections showed erosion of the superficial epithelium. The villi were infiltrated with round cells, many of which were lymphocytes and young myeloid cells. The muscular wall, particularly close to the serosal surface, showed focal areas of infarction surrounded by an accumulation of immature blood cells and occasional megakaryocytes.

Pancreas: The pancreas weighed 100 Gm. and was grossly normal. Microscopically, the acinar and islet cells were normal. There were considerable periductile and perivascular fibrosis and a thickened zone of periglandular fibrosis infiltrated by red cells.

Adrenal Glands: The adrenal glands appeared somewhat enlarged and firm, and the left was incorporated in the scar tissue adjacent to the previously removed spleen. The cut surface revealed thickening of the medulla and numerous tiny grayish white nodules.

The sections showed a thickened capsule. The cortical cells and cords were separated and replaced with connective tissue which was partially hyalinized. There were foci of necrosis surrounded by zones of hemopoiesis. The medullary

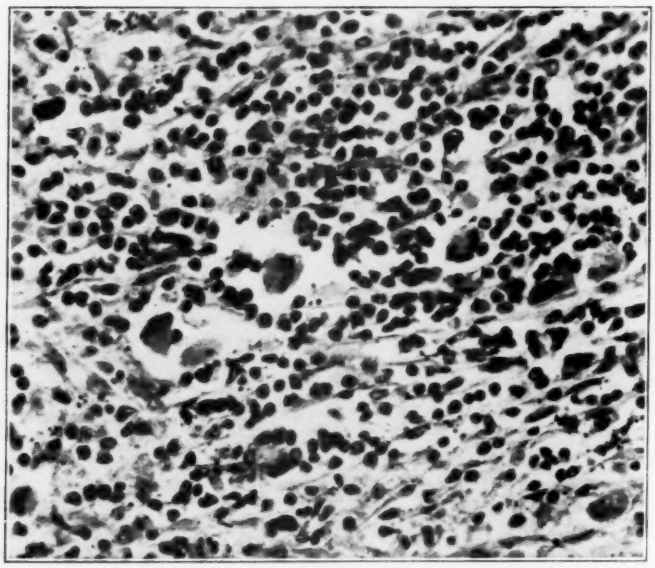

Fig. 4.—Photomicrograph of spleen. The sinuses are dilated and contain numerous megakaryocytes, many myeloblasts, a few lymphocytes, red blood cells and much debris.

zone was replaced by connective tissue, and only a few chromaffin cells remained. Scattered throughout the connective tissue were many large myeloblastic cells. The capillaries were distended, and there was hemorrhage into many of the necrotic foci. An occasional capillary was occluded by a thrombus. Numerous acid-fast bacilli were found in the necrotic areas.

Urinary Tract: The right kidney weighed 220 Gm. The external surface showed a slight lobulation. The cut surface revealed a cortex of normal thickness. The medullary zone was pale. The markings were somewhat indistinct. The pelvis was normal. The capsule stripped with ease. The left kidney weighed 215 Gm. and grossly was similar to the right, except for a single grayish white nodule measuring 4 mm. located in the upper pole. The ureters were normal.

The bladder appeared grossly normal except for the peritoneal surface previously described.

Microscopically the glomeruli and tubules showed many early degenerative changes, probably post mortem in character. There was considerable perivascular fibrosis. An infarct was found which showed caseation, necrosis and round cell infiltration. Huge numbers of acid-fast bacilli were demonstrated by special staining.

The surface of the bladder was covered with a thick fibrinocellular exudate containing large numbers of immature blood cells of all forms and occasional megakaryocytes. Some of these cells were found between the muscle bundles.

Genital Tract: The uterus, tubes and ovaries were covered with grayish white nodules on their peritoneal surfaces but were otherwise normal.

Breast: The breasts were normal.

Bone (fig. 5 and 6): The cortex of the ribs, sternum and vertebra was thickened and the trabeculae of cancellous portions were prominent. Firm white fibrous tissue obliterated the medullary spaces in the sectioned ribs. In the sternum and vertebra the medullary portion was filled with a uniform pinkish tissue.

The most pronounced change under the microscope was the extensive fibrosis which apparently had replaced the normal marrow. Scattered throughout the fibrous tissue were many megakaryocytes and myeloblasts and a few megaloblasts. Infarcted and necrotic zones which contained many acid-fast bacilli were found.

Lymph Nodes: The mediastinal, retroperitoneal and prevertebral lymph nodes were enlarged and matted together. The mesenteric nodes were slightly enlarged. All of these nodes cut with increased resistance and showed a uniform pink surface. Microscopic study of these lymph nodes recalled the findings in the sections prepared from the bone marrow. The resemblance to Hodgkin's disease under the low power was striking. There were pronounced fibrosis and an infiltration of myeloblasts, erythroblasts and megakaryocytes. Multinucleated cells resembling Sternberg-Reed cells were present. Some of the nodes were clearly necrotic, and the necrotic foci everywhere contained acid-fast bacilli.

Gallbladder: The gallbladder was apparently normal.

Brain: Gross and microscopic examinations of the brain revealed extensive congestion. No nodules similar to those previously described were found.

Pathologic Diagnosis: The pathologic diagnosis was of myelofibrosis, splenomegaly and megakaryocytic myelosis and miliary tuberculosis.

Anatomic Findings: Hemopoietic organs. There were myelofibrosis, extramedullary hemopoiesis and a leukemoid reaction with megakaryocytosis. The spleen had been removed surgically, the lymph nodes were enlarged, the liver was enlarged with fibrosis and there was miliary tuberculosis.

COMMENT

The essential observations in this case were: (1) an apparently well and normal 36 year old woman previous to her delivery on Oct. 11, 1944; (2) a chronic progressive illness associated with splenomegaly discovered immediately post partum; (3) appearance of a typical myelogenous leukemia with megakaryocytosis; (4) observation at necropsy of myelofibrosis, extramedullary hemopoiesis and atypical miliary tubercles massively infested with acid-fast, gram-positive bacilli, and (5) absence of typical leukemic infiltrations.

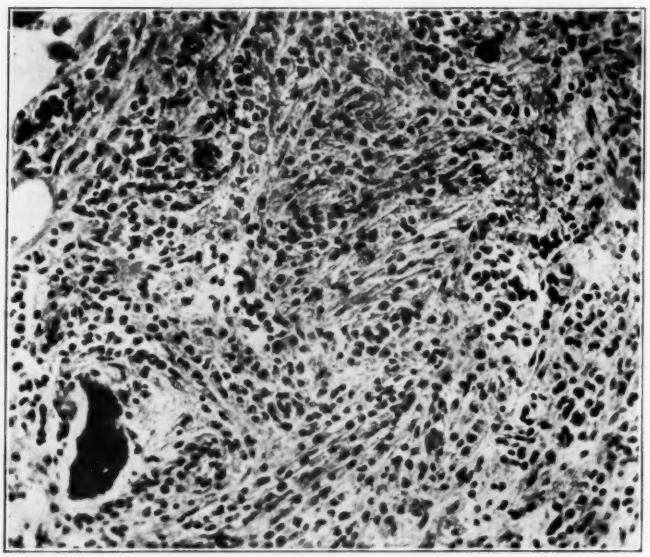

Fig. 5.—Photomicrograph showing extensive myelofibrosis seen in the vertebra.

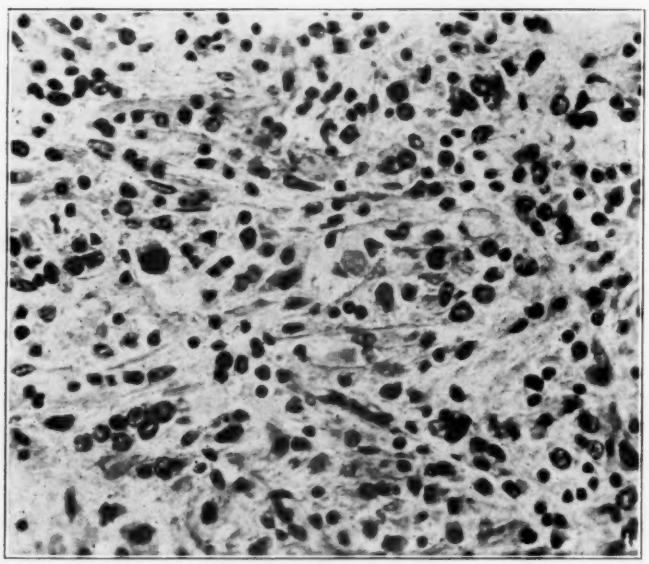

Fig. 6.—Higher magnification of the bone marrow in figure 5. Fibrous tissue replaces most of the normal myeloid elements.

The clinical course was interpreted as an unusually acute phase of myelogenous leukemia presenting the added complication of possible embolism and infarction because of the extremely high platelet count. The presence of tuberculosis was not considered likely. Even at necropsy the multitude of tiny, grayish white nodules did not resemble tubercles but rather leukemic nodules. Only after microscopic examination, when the nodules were found not to be leukemic, was the possibility of tuberculosis considered.

Carpenter and Flory [1b] reported a case of splenomegaly with a leukemic blood picture similar in every detail to the case presented here. They described the firm, grayish nodules in the lung filled with acid-fast bacilli and bone marrow lesions microscopically similar. They attributed the miliary tubercles to a coincidental terminal miliary tuberculosis. In their case 1 Churg and Wachstein [8] described pinhead-sized abscesses in the lung and liver. These abscesses were surrounded by a collection of myeloid cells. In their case 3 similar lesions were seen. The lungs in this case presented healed primary tuberculosis with calcified lymph nodes and no leukemic infiltrations. No interpretation was offered in these cases for the abscesses nor was the presence of an organism or its type determined. Similarly, Taylor and Smith [4] reported a patient with pronounced foci of necrosis in the liver, and in some of these areas formation of young fibrous tissue was demonstrated. Here again there was no interpretation of the necrotic foci. Heinle and Weir,[9] on the other hand, reported a case of "morphologic obliteration of chronic myeloid leukemia by active tuberculosis." At autopsy leukemic infiltrations of the various organs as encountered in true leukemia were not observed. Acid-fast organisms were found but were not further identified by culture or other means. Krasso and Nothnagel [10] reported generalized miliary lesions resembling anemic infarcts and filled with many acid-fast organisms in a case believed to be of myelogenous leukemia. The character of these organisms was disputed by subsequent investigators. Klemperer [11] stated, "In myeloid leucemia with predominance of megakaryocytes within the spleen, I have seen the giant cells in conspicuous abundance at the periphery of anemic infarcts."

8. Churg, J., and Wachstein, M.: Osteosclerosis, Myelofibrosis and Leukemia, Am. J. M. Sc. **207**:141, 1944.

9. Heinle, R. W., and Weir, D. R.: Morphologic Obliteration of Chronic Myeloid Leukemia by Active Tuberculosis: Report of a Case, Am. J. M. Sc. **207**:450, 1944.

10. Krasso, H., and Nothnagel, H.: Atypische Tuberkulose (Geflügeltuberkulose?) bei myeloischer Leukämie, Wien. Arch. f. inn. Med. **11**:507, 1925.

11. Klemperer, P., in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 1651.

This is the same pathologic picture seen in miliary lesions in the case presented here.

Flory and Carpenter,[1b] in reviewing a series of cases of this type, pointed out their similarity and concluded that the syndrome of nonleukemic myelosis may be due to "chronic progressive hyperplasia of multipotential mesenchymal tissues caused by an unknown stimulus." The observations in the case reported here suggest that this unknown stimulus could be the acid-fast organisms found in such huge numbers in the miliary lesions. Further studies, unfortunately, were not undertaken at the time of necropsy to identify the exact nature of these acid-fast organisms.

Judging from other case reports in the literature and careful pathologic studies by such workers as L'Esperance and Branch, it is possible that these cases represent the result of human infestation by avian tuberculosis. If the lesions in this case represent tubercles, they are highly atypical and pathologically suggest lesions found experimentally in avian tuberculosis. L'Esperance[12] devoted considerable time and energy to the pathogenicity of avian tuberculosis and its possible relationship to Hodgkin's disease. Branch[13] reviewed much of her work and the literature on the avian tubercle bacillus, concluding that it can infect man. Löwenstein[14] quoted reports on 4 cases of myelogenous leukemia from which avian tubercle bacilli were recovered. Krasso and Nothnagel[10] stated their belief that the acid-fast bacillus in their case was avian tuberculosis. Branch[13] pointed out the following characteristics of avian tuberculosis from his review of the literature: (1) there is a long-continued remittent fever with elevation of the temperature in the evening; (2) a splenic tumor is almost always present; (3) the liver is frequently enlarged; (4) the bone marrow, kidneys, lymph nodes and skin are frequent sites of involvement; (5) the lungs have multiple grayish nodular foci; (6) there is a complete absence of proliferative changes and caseation, and (7) there are large numbers of tubercle bacilli (predominantly intracellular) in the focal lesions.

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12. L'Esperance, E. S.: Experimental Innoculation of Chickens with Hodgkin's Nodes, J. Immunol. **16**:37, 1929; Pathogenicity of Avian Tubercle Bacillus, ibid. **16**:27, 1929; Study of Case of Hodgkin's Disease in Child, ibid. **18**:127, 1930.

13. Branch, A.: Avian Tubercle Bacillus Infection with Special Reference to Mammals and to Man: Its Reported Association with Hodgkin's Disease, Arch. Path. **12**:253 (Aug.) 1931.

14. Löwenstein, E.: Ueber Septikämie bei Tuberkulose, Ztschr. f. Tuberk. u. Heilstättenw. **7**:491, 1905; Ueber das Vorkommen von Geflügel-Tuberkulose beim Menschen, Wien. klin. Wchnschr. **26**:785, 1913; Das Krankheitsbild der Hühnertuberkulose beim Menschen, Ztschr. f. Tuberk. **41**:18, 1924; Das Krankheitsbild der Hühnertuberkulose beim Menschen, Med. Klin. **24**:1782, 1928.

It is possible that acid-fast organisms other than forms of tuberculosis may give rise to characteristic infections in man. Among these are the various actinomycoses. Cobbett [15] cultured acid-fast organisms of an undetermined variety from lesions on a soldier in 1918.

It is not the purpose of this paper to propose the origin of this syndrome or to affirm that it is a form of tuberculosis, but rather to bring this possibility to the attention of others and to encourage a definite search for this etiologic factor in subsequent cases.

SUMMARY

Numerous cases of splenomegaly presenting the same clinical and pathologic features but bearing a variety of titles and interpretations are reported in the literature.

A report is given of a case of splenomegaly, hepatomegaly, a leukemoid blood picture, megakaryocytosis, extramedullary hematopoiesis, myelosclerosis and atypical miliary tuberculosis.

It is suggested that the entire syndrome may be due to the acid-fast organism seen in the miliary lesion which pathologically resembles avian tuberculosis.

Captain Otis Wildman (MC) U.S.N. and Commander C. F. Geschickter (MC) U.S.N.R. assisted in the pathologic study of this case. The photographs were made by Lieutenant (jg) J. R. Borland (HC) U.S.N.R. The clinical material was furnished by Lieutenant Commander G. R. Lamb (MC) U.S.N.R.

710 Lake Shore Drive, Chicago, Ill.

15. Cobbett, L.: An Acid Fast Bacillus Obtained from a Pustular Eruption, Brit. M. J. **2**:158, 1918.

EFFECT OF ATROPINE ON THE BRANHAM SIGN IN ARTERIOVENOUS FISTULA

MAJOR MILTON L. KRAMER
AND
CAPTAIN JACOB W. KAHN
MEDICAL CORPS, ARMY OF THE UNITED STATES

THE BRANHAM [1] sign is of proved value in the diagnosis of arteriovenous fistulas. It consists of a slowing of the pulse rate on temporary obliteration of the fistula. The response to obliteration is prompt, occurring within seconds, suggesting a reflex arc with the vagus nerve as the efferent limb. It would seem possible, therefore, to eliminate the Branham phenomenon in patients with arteriovenous fistulas by paralysis of the vagus nerve induced by atropine. This has been attempted previously with variable results.[2] In the light of our experiences, this variability appears related only to the degree of completeness of the atropine effect attained.

PROCEDURE

The subjects were soldiers who had sustained wounds which led to the development of arteriovenous fistulas. A solution of atropine sulfate in distilled water was administered intravenously. The doses varied from 1.7 to 1.95 mg. of the drug. In an earlier case, the administration of three successive doses of 0.065 mg. of atropine sulfate failed to induce as striking an effect as did the single administration of the entire dose. In this study the latter procedure was employed in all except case 9, in which initial tachycardia warranted caution.

Observations were made on heart rate, pupillary changes and dryness of the mouth as evidence of atropinization. The changes in heart rate and pupillary size usually appeared within three minutes. The dryness of the mouth was slower in development. The subject was recumbent during the period of observation and had rested for fifteen to thirty minutes before basal studies were made. The heart rate was counted for a full minute with the stethoscope, and the blood pressure was determined by the use of a mercury manometer with check readings. Manual obliteration of the fistula was judged complete on disappearance

From the Vascular Surgery Center, Ashford General Hospital.

1. Branham, H. H.: Aneurismal Varix of the Femoral Artery and Vein Following a Gunshot Wound, Internat. J. Surg. **3**:250, 1890.

2. (*a*) Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurism, Heart **10**:301, 1923. (*b*) Elkin, D. C.: Arteriovenous Aneurysm, J. M. A. Georgia **25**:417, 1936.

of the bruit at the site of the fistula. None of the subjects had a sensitive carotid sinus mechanism.

As is seen in the accompanying chart, there was a considerable fall in the pulse rate on obliteration of the fistula prior to atropinization.

CASE & DIAGNOSIS	CONTROL		DURING OBLIT. OF FISTULA		EFFECT OF ATROPINE						
	PULSE	B.P.	PULSE	B.P.	DOSE & REACTION	TIME IN MINUTES AFTER INJECTION					
						3	5	8	11	15	
No. 1 Arteriovenous Fistula Popliteal Vessels	74	133/66	56	130/84	1.95 mg. wide pupils no oral dryness	128	132	132	126	120	Pulse Control
						170/100	158/108	150/100	148/98	144/96	B.P.
						120	126	122	124	120	Pulse During Oblit.
						170/114	170/114	150/110	154/108	144/110	B.P.
No. 2 Arteriovenous Fistula Popliteal Vessels	84	118/74	62	120/88	1.95 mg. wide pupils dryness ++	120	120	120	122	120	Pulse Control
						136/94	136/94	132/94	130/90	126/90	B.P.
						120	120	120	120	118	Pulse During Oblit.
						136/104	132/94	134/98	130/96	130/96	B.P.
No. 3 Arteriovenous Fistula Axillary Vessels	72	150/74	64	156/90	1.95 mg. wide pupils dryness +++	118	118	118	114	118	Pulse Control
						150/90	140/90	142/90	142/98	134/90	B.P.
						110	112	108	112	108	Pulse During Oblit.
						158/108	150/110	156/110	150/110	150/110	B.P.
No. 4 Arteriovenous Fistula Femoral Vessels	80	124/60	62	140/84	1.95 mg. wide pupils dryness +	124	120	124	124	126	Pulse Control
						150/80	140/80	144/78	134/78	140/78	B.P.
						124	120	124	124	122	Pulse During Oblit.
						180/110	178/112	178/116	170/120	166/114	B.P.
No. 5 Arteriovenous Fistula Brachial Vessels	72	124/56	60	124/68	1.95 mg. Very wide pupils dryness +++	110	110	108	106		Pulse Control
						140/70	134/70	130/68	130/70		B.P.
						106	108	104	104		Pulse During Oblit.
						140/70	136/82	136/80	136/80		B.P.
No. 6 Arteriovenous Fist. Common Carotid Artery; Int. Jugular Vein.	98	122/60	84	122/70	1.95 mg. wide pupils dryness ++	136	130	122	128		Pulse Control
						110/68	110/70	110/70	106/66		B.P.
						128	130	120	124		Pulse During Oblit.
						112/74	114/80	114/75	112/74		B.P.
No. 7 Arteriovenous Fistula Femoral Vessels	96	120/50	60	120/70	1.7 mg. wide pupils dryness +	128	124	120	120		Pulse Control
						118/60	108/60	108/60	110/60		B.P.
						120	120	118	116		Pulse During Oblit.
						122/60	124/80	120/60	120/60		B.P.
No. 8 Arteriovenous Fistula Femoral Vessels	78	116/66	60	120/70	1.95 mg. wide pupils dryness ±	112	110	120	110		Pulse Control
						120/70	118/74	110/72	110/70		B.P.
						108	110	110	106		Pulse During Oblit.
						124/90	120/90	122/90	116/92		B.P.
No. 9 Arteriovenous Fistula Femoral Vessels	140	140/76	120	134/90	1.0 mg. wide pupils dryness ++	176	180	160	156		Pulse Control
						120/74	124/76	120/78	118/60		B.P.
						178	178	168	160		Pulse During Oblit.
						124/68	122/90	116/90	116/90		B.P.
No. 10 Arteriovenous Fistula Posterior Tibial Vessels	80	124/80	70	124/88	1.95 mg. wide pupils dryness ++	80		76	102		Pulse Control
						120/76		118/80	116/80		B.P.
						72		84	98		Pulse During Oblit.
						130/86		116/90	116/90		B.P.

Results of atropinization studies; the symbols +++, ++, + and ± represent decreasing degrees of oral dryness.

This is listed as the control reading. There is likewise shown the failure to obtain this fall in the pulse rate after atropinization except in case 10.

Of correlated interest were the associated changes in blood pressure following obliteration of the fistula prior to atropinization. Usually the

systolic pressure rose slightly or remained unchanged and the diastolic pressure invariably rose. The effect on blood pressure of atropine alone in the dosage employed was inconstant and usually not striking. In this group 4 patients showed significant increases in systolic pressure (especially in cases 1 and 4), 3 showed a decrease and 3 showed no appreciable change. All but 2 of the patients showed an increase in diastolic pressure. The pulse pressures were not significantly altered from the levels measured before atropinization. However, obliteration of the fistula during atropinization led to a further rise in diastolic pressure in every instance. The pulse pressures were reduced in all but case 4, in which an unusual rise in the systolic pressure served to compensate for the pronounced rise in diastolic pressure. In other words, the changes in blood pressure usually associated with obliteration of a fistula—namely, rise of diastolic pressure and reduction of pulse pressure—were not influenced by atropine. These data are presented in the chart.

From these observations it appears conclusive that atropine in adequate dosage is capable of preventing the slowing of the pulse that follows obliteration of an arteriovenous fistula. Case 9 was of special interest in that despite an initial tachycardia a fair Branham's sign was elicited before atropinization. A low grade vagal tone was still present, however, since a dose of 1 mg. of atropine was able to increase the rate further and to eliminate the Branham sign. In case 10 there was failure to show the development of any appreciable tachycardia, and it was suggested that for this patient, who weighed 235 pounds (106 Kg.), the dosage of atropine given was adequate.

COMMENT

One can only conjecture as to the physiologic explanation for the Branham phenomenon. It has been suggested that the bradycardia follows a sudden pronounced increase in circulating blood in the general circulation on elimination of the short circuit and a consequent sudden increase in blood pressure and stimulation of the carotid sinus mechanism. This theory postulates a preceding increase in the volume of circulating blood sufficient to produce the effect. The fact that the Branham phenomenon is noted promptly after the development of the fistula raises some question of the validity of the theory in this connection. Although in general patients with the larger fistulas show the most striking changes in pulse rate, the phenomenon is usually, and as strikingly, observed in patients with small fistulas. Studies of the blood volume, too, have not been in agreement, although it appears likely that in persons with fistulas of long standing or in those with large fistulas an increased blood volume is present. Those with fistulas of short duration or of small size may not show any significant change in blood volume.

PRECORDIAL LEADS IN CHILDREN

A. BATTRO, M.D., and J. C. MENDY, M.D.
BUENOS AIRES, ARGENTINA

IN 1935 Master, Dack and Jaffe [1] carried out the first investigation on precordial leads in 72 healthy children. They recorded seven precordial leads each separated by a distance of 2 cm. at the level of the fourth intercostal space, beginning at the left margin of the sternum, and found that the T wave, initially negative, became positive in the proximities of the apex.

A year later Rosenblum and Sampson [2] recorded in 15 children the chest-back lead and three precordial leads in the second, third and fourth intercostal space at the left margin of the sternum. Contrary to what was shown by their controls (66 records on adults without cardiac lesions in which the T wave was negative), this wave was found to be positive in the precordial leads in 64 per cent of the children, diphasic or isoelectric in 32 per cent and negative in only 4 per cent.

Among 50 normal children Moia [3] found the T wave positive in 56 per cent.

Robinow, Katz and Bohning (1936),[4] recording a single precordial lead in the fourth intercostal space at the left margin of the sternum, found that the T wave was positive in 58 per cent of 61 children of different ages. They arrived at the conclusion that the younger the children the greater the percentage of positive T waves and that at about the age of 14 the precordial electrocardiogram becomes similar to that of the normal adult.

From the National Academy of Medicine, Institute of Physical Research Applied to Human Pathology, Cardiological Section, Prospero Baurin Foundation.

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2. Rosenblum, H., and Sampson, J. J.: A Study of Lead IV of the Electrocardiogram in Children with Especial Reference to the Direction of Excursion of the T Wave, Am. Heart J. **11**:49, 1936.

3. Moia, B.: La IV derivación o derivación torácica en 50 niños normales, Rev. argent. de cardiol. **2**:26, 1935.

4. Robinow, M.; Katz, L. N., and Bohning A.: The Appearance of the T-Wave in Lead IV in Normal Children and in Children with Rheumatic Heart Disease, Am. Heart J. **12**: 88, 1936.

In 1937 Master, Dack and Jaffe [5] studied the precordial leads in 71 children between the ages of 2 and 15 years. They recorded the electrocardiogram from seven points of the precordial region from the right margin of the sternum to the left, placing the electrodes, separated by a distance of 2 cm., in the fourth intercostal space in children under 6 and in the fifth intercostal space in children over 6 years of age. They employed the CF lead. Their results proved: frequent absence of the P wave; P-R interval from 0.1 to 0.14 second; Q of greater voltage and R of less amplitude in points 4, 5, 6 and 7; QRS duration between 0.06 and 0.08 second; R-T with deviations of 1 mm.; T positive and diphasic in 60 per cent of cases in points 4, 5, 6 and 7. They observed also modifications of Q, R and T waves due to respiration and changes of position of the body. In children of 14 to 15 years of age the appearance of the precordial electrocardiogram resembles that of the adult (negative T waves). These authors claim that the positive T wave is a characteristic of the precordial electrocardiogram in children, but due to the fact that either positive or negative T waves may be found, they do not give diagnostic value to the configuration of T. They found no relation between the positivity of T, the electrical axis and the roentgenologic image of the heart.

In all the investigations mentioned in the foregoing paragraphs the precordial leads were taken in such a way that the relative positivity of the precordial electrode is represented by a downward deflection ($\mp$).

Using the modern standardized technic (the relative positivity of the precordial electrode being recorded by an upward deflection ($\pm$), Master [6] believes that the negative T waves are of normal occurrence in the precordial leads of children. Latorre (1941) [7] and Seham and Moss (1942) [8] do not find any clinical value in the precordial lead in children.

MATERIAL

Our work was carried out on 50 healthy children of the Preventorio Rocca, who were divided into three groups: A (0-2 years old), 13 children; B (3-5 years), 16, and C (6-10 years), 21.

5. Master, A. M.; Dack, S., and Jaffe, H. L.: The Precordial Lead of the Electrocardiogram of Normal Children, Am. J. Dis. Child. **53**:1000 (April) 1937.

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7. Latorre, B.: Desarrollo y evolución del electrocardiograma en el lactante normal y prematuro sano, en su primer año de vida, Rev. chilena de pediat. **12**:627, 1941.

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TABLE. 1.—*Amplitude of Ventricular Deflections in Standard and Precordial Leads*

	D_1	D_2	D_3	V_1	V_2	V_3	V_4	V_5	V_6
Group A, 0-2 years									
Q wave									
Minimum	0	0	0	0	0	0	0	0	0
Maximum	2	3	4	0	0	0	1	6	3
Medium	0.7	1.3	1.6	0	0	0	0.09	0.8	1.05
R wave									
Minimum	0	0	1	7	7	9	9	8	1
Maximum	10	14	11	20	22	17	18	25	15
Medium	4.2	5.7	5.6	12	12	11	11	13	8.3
S wave									
Minimum	0	0	0	0	3	5	4	2.5	1.5
Maximum	7	5	3.5	16	15	10	13	12	10
Medium	3.9	2.7	1.1	6.3	6.4	7.7	8.4	6.6	4
T wave									
Minimum	0.5	1	0	0.5	0.5	1	0.5	0.5	1
Maximum	5	4	3	6	4.5	4.5	4	6	6
Medium	2.6	2.4	0.2	2.1	1.2	0.2	0.4	2.1	2.3
R-S or QSR waves									
Minimum	5	2.5	3	7	13	16	17	5.5	3
Maximum	17	16	11	36	32	24	30	31	21
Medium	8.1	8.4	6.7	20	20.2	10.5	20.2	19.3	2.09
Group B, 3-5 years									
Q wave									
Minimum	0	0	0	0	0	0	0	0	0
Maximum	1	2	3	0	0	0	2.5	3	2.5
Medium	0.1	0.3	1.4	0	0	0	0.3	0.8	0.7
R wave									
Minimum	2	3	2	2	5	5	5	7.5	5
Maximum	10	12	10	9	16	20	22	22.5	18.7
Medium	5	7.6	5.6	5.5	9.5	11	13	14	9.1
S wave									
Minimum	0	0	0	2.5	5	3	3	0	0
Maximum	6	4	5	15	22.5	21	18	10	5
Medium	2.5	1.6	0.8	7.1	12	11	10	5.5	2.2
T wave									
Minimum	0	0.5	0	0.5	0.5	0.5	0.5	2	1
Maximum	4	4	1.5	4	4	7.5	8.5	6	6
Medium	1.7	1.8	0.2	1.9	0.4	1.9	1.9	2.7	2.2
R-S or QSR waves									
Minimum	3	4	2	5	15	8	10	8	5
Maximum	15	12.5	12	24	37.5	34.5	33.7	28	23.7
Medium	7.6	9.1	6.5	12.6	22.9	23.7	23.9	19.2	10.7
Group C, 6-10 years									
Q wave									
Minimum	0	0	0	0	0	0	0	0	0
Maximum	2	3	3	0	0	1	1.5	4	3
Medium	0.2	0.5	0.6	0	0	0.4	0.2	0.6	0.4
R wave									
Minimum	2	3	0.5	1	2	4	5	5	3
Maximum	9	13	13	8	14	18	17	17	12
Medium	5	7.2	4.2	4	7.4	10	11	9.9	7.1
S wave									
Minimum	0	0	0	1	3	3	1	0.5	0
Maximum	3	3.5	4	15	17.5	17.5	21	13	5
Medium	1.6	1.4	0.7	7.4	8.9	9.5	7.6	4.1	1.8
T wave									
Minimum	0.5	0.5	0	0.5	0.5	0.5	0.5	0.5	0.5
Maximum	4	5	1	2.5	3	5	5	4.5	4
Medium	2	2.1	0.1	1	0.1	1.6	2.3	2.3	1.7
R-S or QSR waves									
Minimum	3	5	2	2	8	11	10	5.5	4
Maximum	13	13	13	18.5	31	28.5	32.2	28.5	14
Medium	6.6	8.7	5	11.4	17.6	19.7	19	14	8.9

TECHNIC

Besides the "standard" leads (I, II and III) six precordial leads were recorded following the specifications of the Committee of the American Heart Association. The Wilson terminal electrode was used (V_1, V_2, V_3, V_4, V_5 and V_6) as well as the unipolar limb leads (V_R, V_L and V_F).

RESULTS

Table 1 shows the measurements of the different waves recorded in the mentioned leads for the three groups of ages, and table 2 a comparison of these values with those of adults. We shall make special

TABLE 2.—*Mean Voltage of the Different Waves in Multiple Precordial Leads in Children and Adults*

		Wave				
		Q	R	S	T	R-S
V_1	0-2 years	0	12	6.3	2.1	20
	3-5 years	0	5.5	7.1	1.9	12.6
	6-10 years	0	4	7.4	1	11.4
	Adults	0	4.16	11.05	1.23	15.21
V_2	0-2 years	0	12	6.4	1.2	20.2
	3-5 years	0	9.5	12	0.4	22.9
	6-10 years	0	7.4	8.9	1.1	17.6
	Adults	0	9.05	16.23	6.22	25.27
V_3	0-2 years	0	11	7.7	0.2	18.7
	3-5 years	0	11	11	1.9	23.7
	6-10 years	0.4	10	9.5	1.6	19.7
	Adults	0.013	16.70	9.05	6.26	25.75
V_4	0-2 years	0.09	11	8.4	0.4	20.2
	3-5 years	0.3	13	10	1.9	23.9
	6-10 years	0.2	11	7.6	2.3	19
	Adults	0.37	22.31	5.32	5.66	27.63
V_5	0-2 years	0.8	13	6.6	2.1	19.3
	3-5 years	0.8	14	5.5	2.7	19.2
	6-10 years	0.6	9.9	4.1	2.3	14
	Adults	0.57	18.78	1.93	4.59	20.70
V_6	0-2 years	1.05	8.3	4	2.3	12.3
	3-5 years	0.7	9.1	2.2	2.2	10.7
	6-10 years	0.4	7.1	1.8	1.7	8.9
	Adults	..	5.81	6.09	2.55	11.91

The values for adults have been taken from "Nomenclature and Criteria for Diagnosis of Diseases of the Heart," 1939.

reference in this paper to the precordial leads (V_1, V_2, V_3, V_4, V_5 and V_6), which showed the following principal characteristics:

Group A (0 to 2 Years).—The electrocardiographic peculiarities of this group were:

(1) Absence of the Q wave up to V_3.

(2) R wave of great amplitude, larger than S in most cases in V_1 (fig. 1). The maximum height obtained in V_1 was 20 mm. and its average value 12 mm. These figures persist without great variations up to V_5 and decrease in V_6 to a middle value of 8.3 mm.

(3) S wave of a relatively small amplitude in V_1. It increases gradually up to V_4 and decreases in V_5 and V_6 (fig. 2). Certain equilibrium or diphasism R-S may be observed in some cases in the right precordial leads (fig. 3).

(4) T wave frequently negative or diphasic ($\mp$) in the first three leads (in V_1 90 per cent, V_2 85 per cent and V_3 55 per cent), then less

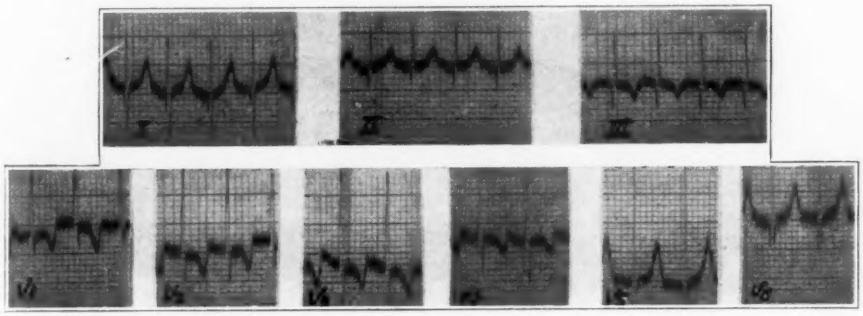

Fig. 1.—Electrocardiogram of a 33 day old child. The R wave has great amplitude in V_1. The T wave is negative in V_1, V_2, V_3 and V_4.

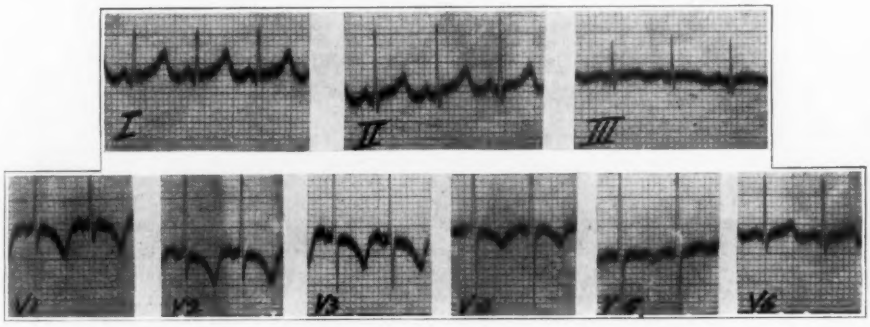

Fig. 2.—Electrocardiogram of a 70 day old child. The S wave is of small amplitude in V_1. The T wave is negative in V_1, V_2, V_3, V_4 and V_5.

frequently negative in the points to the left, although the negativity or diphasism persisted frequently (20 per cent of cases) even to V_6 (fig. 4). The negativity or diphasism of T is sometimes decided. Generally the obliqueness of the descendant branch is greater than that of the ascendant one, and the junction of both branches under the isoelectric level is the vertex of an acute angle.

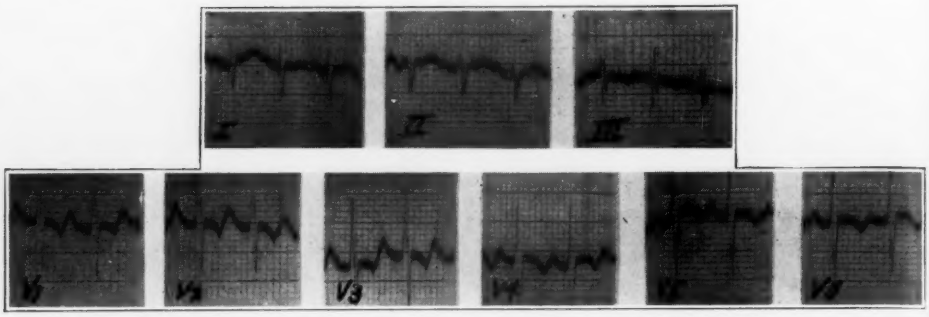

Fig. 3.—Electrocardiogram of a 30 day old child. The R and S waves are of nearly equal voltage in the precordial leads. Negativity (diphasism ±) of the T wave is shown in all the precordial leads.

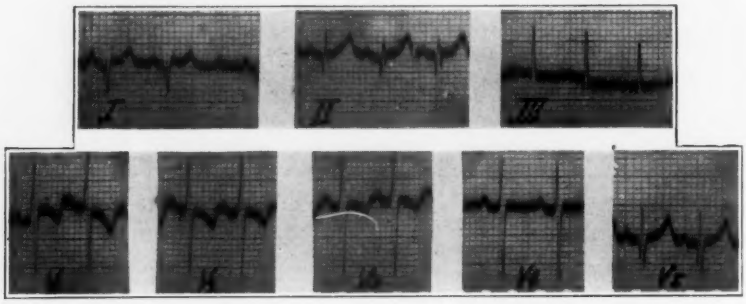

Fig. 4.—Electrocardiogram of a 20 day old child. The R and S waves are of nearly equal voltage in V_1 and V_2.

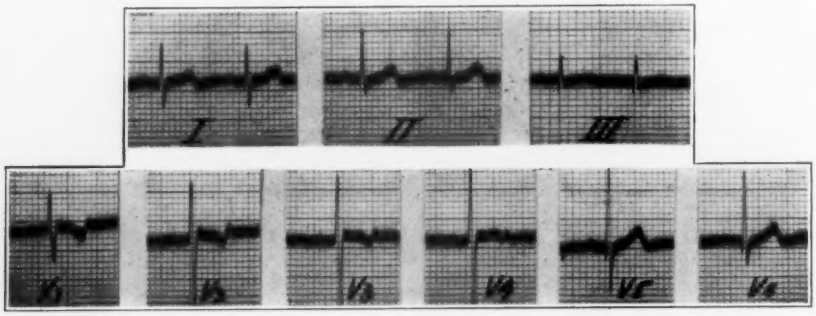

Fig. 5.—Electrocardiogram of a 4 year old child. The R wave increases up to V_5; the S wave increases up to V_4 and decreases in V_5 and V_6. The T wave in V_1, V_2, V_3 and V_4 is diphasic.

Group B (3 to 5 Years).—This group showed the following characteristics:

(1) Absence of Q up to V_3, as in group A.

(2) R wave of appreciably less amplitude in V_1 than in group A, increasing progressively in V_2, V_3, V_4 and V_5, and decreasing in V_6.

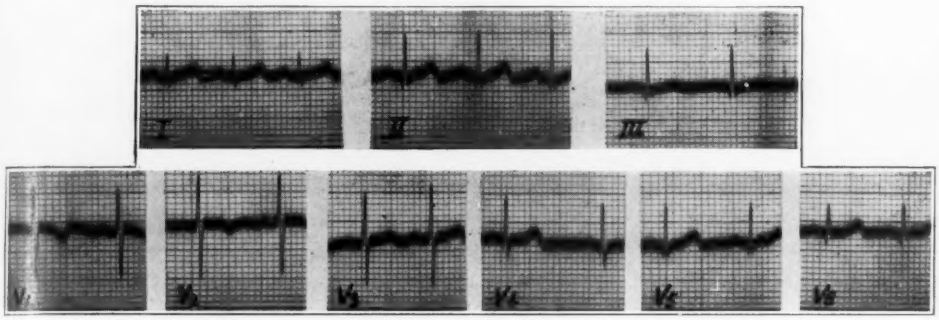

Fig. 6.—Electrocardiogram of a 3 year old child. The R and S wave are of nearly equal voltage in V_1, V_2 and V_3. The T wave is negative in V_1 and V_2.

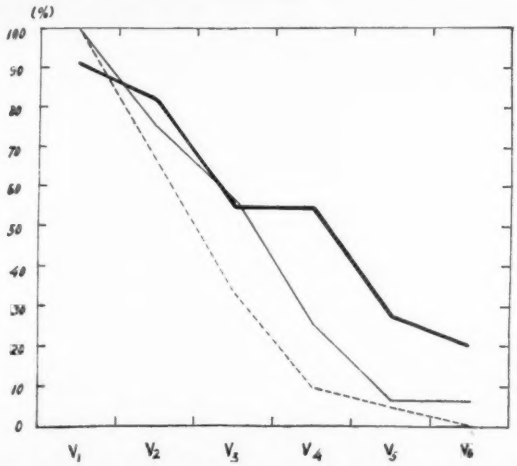

Fig. 7.—Frequency of the diphasic T waves in groups A, B and C. The wide black line is for children from birth to 2 years of age; the narrow black line for children from 3 to 5 years of age, and the broken line for children from 6 to 10 years of age.

(3) The S wave to a certain extent similar to that of the adults. It was of less amplitude in V_1 and V_2 and increased comparatively after V_3 until it exceeded the size found in the adult. In V_6, however, its size was smaller than that of the S wave in the adult (fig. 5).

(4) T wave with similar characteristics to that of group A, although its negativity was much more unusual in V_5 and V_6 (5 per cent).

Certain equilibrium or isodiphasism between R and S may be frequently observed in the right precordial leads in this group (fig. 6).

Group C (6 to 10 Years).—In this group were observed:

(1) Absence of Q up to V_2 as in adults.

(2) R wave of smaller amplitude in V_1 but increasing more evidently than in the former group up to V_4 and resembling what is commonly seen in the adults (fig. 6).

(3) S of higher voltage than R. The modifications undergone by this wave in the precordial leads resemble those occurring in adults, although the changes of height are not so definite.

(4) The T wave was found to be positive in the points to the left of the sternum but the negativity or diphasism of the T wave may be present in 10 per cent of the cases in V_4.

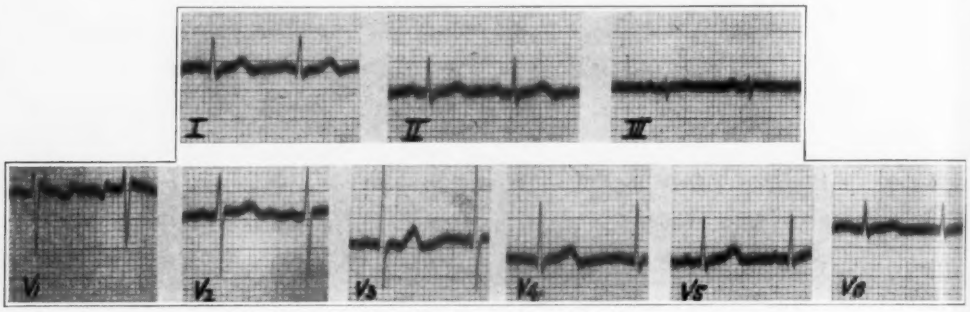

Fig. 8.—Electrocardiogram of a 7 year old child. It resembles the adult type.

A peculiarity that concerns the three groups is that in the precordial leads V_1 to V_6 the negativity of T observed in one lead is seldom more pronounced in the following ones; on the contrary, it generally decreases except in the transition from V_1 to V_2.

Figure 7 shows the frequency of negativity or diphasism of the T wave, according to age.

COMMENT

In group A, the R wave was many times found greater than S in V_1; this predominance of the R wave frequently persists up to V_5, differing thus appreciably from the precordial electrocardiogram of the adult. In group B, the R and S waves tend to be of equal amplitude in the leads to the right. They represent a form of transition between the former group (A) and the following (C). In group C the relative size of R and S is fairly similar to the "adult type," with definite predominance of S over R in V_1 and of R over S in V_6.

As regards the behavior of the T wave, it is clearly illustrated in the corresponding diagram.

In the course of years the precordial electrocardiogram of children shows more and more the characteristics observed in the adult, so that it seems apparent that its gradual changes are related to the general development, and especially to the growth of the heart. Concerning this, the changes of position of the heart, its relations with the thorax and the cardiac configuration are of primary importance.

Regarding its position and relations with the thorax, the heart of the child has the following peculiarities:

(1) Greater proximity of the heart to the thoracic wall.

(2) Greater thinness of the thoracic wall.

(3) Greater surface of contact between the thoracic wall and the right ventricle.

(4) No interposition of the lung between the heart and the wall of the thorax.

(5) More elevated diaphragm and consequently more horizontal position of the heart; this inclination begins to lessen between 6 and 12 months of age due to the unequal growth of the thoracic wall in relation to the growth of the lungs and the spine. The gradual lowering of the diaphragm contributes to the subsequent verticalization of the heart.

As regards the influence of the cardiac configuration on the electrocardiogram of the child, one must remember the proportions between the different cardiac cavities and their subsequent modifications.

In the beginning of extrauterine life the auricles are greater than the ventricles. The size and thickness of the right and the left ventricles are practically the same. At the age of 6 years the right ventricles maintain their initial thickness (3 to 4 mm.), while the thickness of the left ventricles has increased gradually to 8 mm.

It has been determined that in the newly born the ratio of the weight of the left ventricle to that of the right ventricle is 1 : 3, against 2 : 26 in the adult.

Concerning the spreading of the electrical impulse one should remember that the activation of the subendocardial region takes place rapidly because it is supplied by a special system of fibers for the conduction of the stimulus (Purkinje tissue). Then the myocardial wall is activated from the subendocardium to the subepicardium. As the conduction of this impulse is made by the cardiac fibers the activation here requires more time. The unipolar electrode placed in a point near the subepicardial region records the currents coming to it, and those leaving it as well, the former as a positive wave (R), the latter as a negative wave (S).

If one considers for instance the position V_1 in the adult, the walls of the right ventricle being appreciably less thick than those of the left, its activation is completed before that of the left (in spite of beginning almost simultaneously in both ventricles). Then the intrinsic R wave of relatively small amplitude is followed by the S. wave (which is the exponent of all the points of the left ventricle not yet activated), and the greater the thickness of the walls of this ventricle, the more important will be the voltage of the S wave. The inverse result is observed in V_6, and in the intermediate points a range of transitional configurations will be observed.

The variations of the precordial electrocardiogram of children will thus depend on the aforementioned circumstances, among which we assign the greatest importance to the unequal development of both ventricles.

In group A, owing to the relative hypertrophy of the right ventricle there is a predominance of the R over the S wave in the points to the right. In group B, in which the predominance of the left ventricle begins to make itself evident, the tendency to isodiphasism R/S is the most outstanding peculiarity.

The negativity of the T wave can also be explained as a result of the different thickness of the ventricles, which modifies the repolarization of the ventricular wall.

In certain pathologic conditions in the adult, associated with hypertrophy of the right ventricle, the T wave becomes negative in the points "to the right"; moreover, the records are very similar to those of groups A and B owing to the simultaneous increased voltage of R.

The physiologic elevation of the diaphragm in children with the corresponding repercussion on the position of the heart is another factor probably influencing the negativity of T. This would be somewhat similar to what happens to a woman in the last months of pregnancy or during a deep complete expiration, when an inversion of the T IV is apt to occur (Master[6]).

The predominant belief that the T wave may be either positive or negative at the apex (T IV) has induced some authors to attribute little diagnostic significance to the precordial electrocardiogram of the child.

The variability of its shape in the different precordial leads and the modifications related to age make it necessary to record it in all the precordial points in order to be able to determine its diagnostic value.

SUMMARY AND CONCLUSIONS

1. The precordial electrocardiogram of a child differs from that of the adult in the characteristics of the QRS complex and of the T wave.

2. The gradual changes undergone by the child's electrocardiogram until it reaches the "adult" type are especially due to the cardiac development.

3. The following are the peculiarities shown by the three groups:

Group A (0 to 2 years): (*a*) Predominance of R over S in V_1; (*b*) frequency of negativity or diphasism of the T wave even up to point V_6.

Group B (3 to 5 years): (*a*) Tendency to isodiphasism of R and S to the right; (*b*) negativity or diphasism of T up to V_6 although less frequently than in the former group.

Group C (6 to 10 years): (*a*) Predominance of S over R in V_1 as in the adult; (*b*) absence of negative T wave in V_5 and V_6, inversely to what is observed in groups A and B.

4. The degree of negativity of T usually decreases gradually in the three groups from points V_1 to V_6 with the exception of V_2, in which the negativity sometimes was greater than in V_1.

5. For the correct interpretation of precordial leads in children the record of all the precordial leads is required.

FATAL MERCURIAL POISONING FOLLOWING PROLONGED ADMINISTRATION OF MERCUROPHYLLINE

SHOLOM O. WAIFE, M.D.
BALTIMORE
AND
PEYTON T. PRATT, M.D.
BROOKLYN

SINCE the introduction of organic mercurial diuretics about twenty-five years ago [1] innumerable injections of such compounds as merbaphen (U. S. P. XI), mersalyl and mercurophylline have been given. Although toxic reactions have been reported they are amazingly few compared to the huge quantities administered. DeGraff and Nadler [2] summarized the literature on toxic manifestations of mercurial diuretics. They reported 26 deaths in sixteen years. No deaths have been reported from administration of the diuretics intramuscularly. Toxic reactions reported fall into three groups. Some reactions were due to the profuse diuresis.[3] Other reactions or death followed suddenly after one or two doses of mercurial diuretics.[4] These were probably the anaphylactoid reaction which might be due to any foreign agent. In some cases, mersalyl apparently caused tubular damage to the kidney.[5]

This case is being reported because, as far as can be determined, it is the first in which there was a mercurial toxic nephrosis with anuria

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From the Departments of Medicine and Pathology of Long Island College of Medicine, Brooklyn, N. Y.

1. Saxl, P., and Heilig, R.: Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjektionen, Wien. klin. Wchnschr. **33**:943, 1920.

2. DeGraff, A. C., and Nadler, J. E.: A Review of the Toxic Manifestations of Mercurial Diuretics in Man, J. A. M. A. **119**:1006 (July 25) 1942.

3. Klinghoffer, K. A.: Dehydration from Diuretics, Internat. Clin. **1**:221 (March) 1941. Poll, D., and Stern, J. E.: Untoward Effects of Diuresis, Arch. Int. Med. **58**:1087 (Dec.) 1936.

4. Cadbury, W. W.: Idiosyncrasy to Salyrgan, in Medical Papers Dedicated to Henry Asbury Christian, Physician and Teacher, in Honor of His Sixtieth Birthday, February 17, 1936, Baltimore, Waverly Press, Inc., 1936, p. 259. Marvin, H. M.: Merbaphen (Novasurol) as a Diuretic in Congestive Heart Failure, J. A. M. A. **87**:1016 (Sept. 25) 1926. Sprunt, D. H.: Renal Damage Following Administration of Merbaphen (Novasurol), Arch. Int. Med. **46**:494 (Sept.) 1930. Wolf, I. J.: Idiosyncrasy to Salyrgan, J. A. M. A. **102**:1177 (April 7) 1934.

5. Rosenthal, M.: The Anatomic Lesions of Fatal Mercurial Intoxication from Salyrgan, Arch. Path. **15**:352 (March) 1933. Tarr, L., and Jacobson, S.: Toxicity of Mersalyl (Salyrgan), Arch. Int. Med. **50**:158 (July) 1932.

and death after the usual course of repeated parenteral injection of mercurophylline.

REPORT OF A CASE

A white woman, 35 years old, was admitted to the Long Island College Hospital on June 2, 1945, for edema of six months' duration. However, the patient had had dyspnea and had been treated with digitalis for twenty years. At 11 she had had chorea, which recurred every year for four years. Then she had several attacks of febrile polyarthritis. From December 1944 to May 20, 1945, she received about 12 injections of mercurophylline with good results; a dose two days before entry had not effected the usual diuresis.

She was an orthopneic, obese woman with a blood pressure of 160 mm. of mercury systolic and 100 diastolic and gave typical evidence of mitral stenosis and auricular fibrillation. The edge of the liver was tender and came 12 cm. caudal to the right costal margin. There was pitting edema of the legs, thighs and sacral region.

She had a trace of protein in the urine, but no casts or red cells; the blood urea was 25 mg. per hundred cubic centimeters, and the glucose, cholesterol, albumin, globulin and hemoglobin were within the normal range. An electrocardiogram was that of a myocardial disease pattern consistent with a clinical diagnosis of mitral stenosis.

On a diet containing very little salt and 1,500 calories per day with digitalis and intravenous mercurophylline injections, 2 cc. every three to five days, her weight fell from 183 (83 Kg.) to 143 pounds (64.9 Kg.) in one month. She was practically free of symptoms and returned to her home. There she received the same dose of mercurophylline intramuscularly once a week, but since there was no real diuresis after the fifth dose, the injection was repeated three days later. After this, oliguria was considerable, edema developed rapidly, and on the third day, after twelve hours of anuria and dull pain in both flanks, she reentered the hospital.

Physical Examination.—The patient on examination was alert, extremely apprehensive but not dyspneic. She had a puffy face and prominent eyes ("nephrotic stare"). Her blood pressure was 135 systolic and 100 diastolic, but subsequent readings could not be obtained because of the edema. The apical rate was 120 per minute and totally irregular, and there was a pulse deficit of 50. Her temperature was 99 F. Fundoscopy showed tortuous veins, but no exudates, hemorrhages or papilledema. The lungs were clear to percussion and auscultation. Her heart was essentially unchanged from the previous entry. The edge of the liver was 7 cm. below the costal margin. The tip of the spleen could be felt. All extremities, thorax, abdomen and face showed considerable pitting edema. There was minimal cyanosis of the nail beds.

Catheterization yielded approximately 8 cc. of turbid, yellow urine, which showed an extreme proteinuria, p_H of 6, 4 white cells, 3 red cells and an occasional granular cast per high power field in the uncentrifuged specimen.

An infusion of 10 per cent glucose in distilled water was started, but because of the considerable edema the infusion occasionally infiltrated the tissues, and during the first eighteen hours only 2,000 cc. were administered. Gradually her extremities became gray, cold and clammy. She complained of sharp pain in both flanks, radiating around to the lower abdominal quadrants.

Her urea nitrogen was 55 mg. per hundred cubic centimeters, and blood urea was 119 mg. per hundred cubic centimeters. An infusion of 20 per cent dextrose

in water was started. Twenty-two hours after the patient's admission a bilateral renal decapsulation was performed with gas-oxygen-ether anesthesia. At operation the capsule of the kidney was very tense. When the capsule was slit the swollen enlarged congested kidneys quickly bulged through. She withstood the operation well, but her face remained flushed. Her extremities were cyanotic and cold. Her blood pressure could not be determined. The pulse was 110 per minute, respirations 30 per minute, temperature 98 F. Postoperatively she received 500 cc. of plasma.

Six hours after operation catheterization yielded 8 ounces (227 cc.) of urine showing considerable albuminuria, hyaline-granular casts and red and white blood cells. The specific gravity was 1.008. Four hours later 4 ounces (113.4 cc.) was obtained of similar composition. However, the patient remained prostrate and semicomatose, and died three hours later.

Postmortem Examination (Seven Hours After Death).—Gross Examination. The body was that of a well developed, somewhat obese, white woman. There was no pertinent information obtained from the external examination except that there was moderate pitting edema of the lower extremities and a large operative incision in each flank.

The pleural cavities each contained 100 cc. of clear yellow fluid. The pericardial cavity contained 30 cc. of clear yellow fluid.

The heart weighed 620 Gm. The left auricle was dilated and the mitral valve was greatly thickened and nodular, with fusion of the valve cusps. The chordae tendineae were thickened and inserted on the under border of the valve. The papillary muscles were considerably hypertrophied, as was the left ventricular wall. The tricuspid valve was similarly involved but to a lesser degree. The aortic valve was not unusual.

The lungs were not edematous, but there were a few small patches of bronchopneumonia.

The peritoneal cavity contained 500 cc. of slightly turbid sanguineous fluid. On the serosal surface of the ileum and large intestine there were focal areas of purple discoloration. The kidneys were in the usual retroperitoneal position, but both capsules had been split.

The essential findings observed in the abdomen were confined to the liver, kidneys and intestines. The liver weighed 2,150 Gm. and was smooth and firm. The cut surface was mottled and yellow-red, and there were several large, focal, hemorrhagic areas measuring 3 cm. to 4 cm. in diameter. The kidneys weighed 350 Gm. each and measured 14 by 9 by 5 cm. They were distinctly swollen, very pale and tan. The cortex was widened, pale and fairly well demarcated from the pale red medullary pyramids. The intestines were not remarkable except for several large areas of hemorrhage in the mucosa of the ileum and colon. There was no urine in the bladder.

Histologic Examination: The microscopic study revealed the following pertinent facts. The heart was noticeably hypertrophied, and there was a moderate perivascular interstitial fibrosis, but there were no Aschoff bodies. There were small areas of bronchopneumonia in the lung. There was chronic passive congestion of the spleen, pancreas and liver.

Sections of the kidney revealed that the general architecture of the kidney was well preserved. The glomeruli were prominent and showed a slight increase in fibrous tissue, but there was no evidence of congestion, atrophy or hyalinization. There was a moderate amount of granular material in Bowman's space. The proximal convoluted tubules showed varying degrees of cellular damage

from cloudy swelling to complete necrosis. A majority of the tubules were patent but moderately filled with an amorphous, eosinophilic granular material. Some cells were swollen and contained granular cytoplasm with large, round, vesicular nuclei, but there were large numbers of the proximal convoluted tubules in which the cellular outlines were lost and the nuclei were absent or pyknotic (fig. 1). This necrosis extended throughout the proximal convoluted tubule. The distal convoluted tubules and collecting tubules were for the most part uninvolved. There were several areas in which small tubules were seen with cuboidal epithelium, hyperchromic elongated nuclei and an occasional mitotic figure. These are regenerating tubules (fig. 2). There was a moderate increase in the interstitial

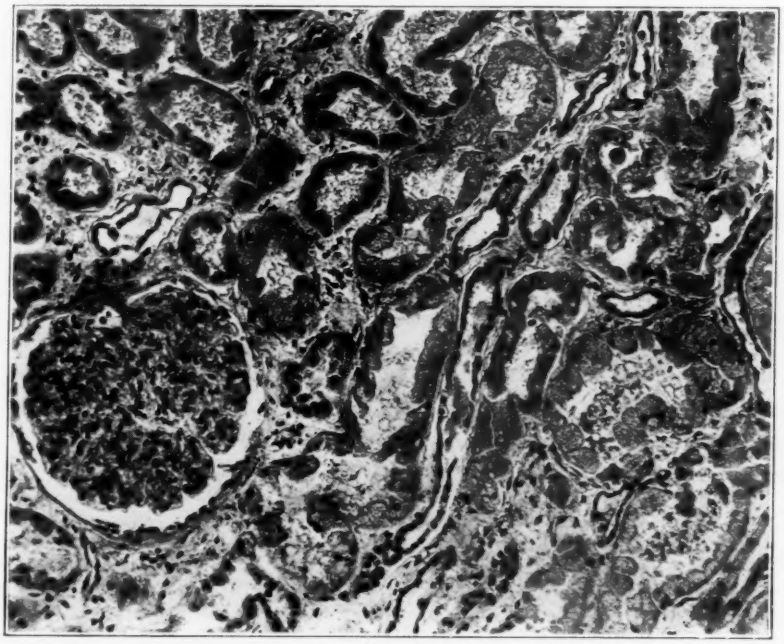

Fig. 1.—The cells of the proximal convoluted tubules are swollen with necrosis of some cells and the absence or pyknosis of many nuclei (× approximately 205).

fibrous tissue. The blood vessels were moderately dilated, and some of the larger vessels had thickened walls which were partially hyalinized. A sudan III stain of the kidney demonstrated in scattered areas a minimal amount of fatty degeneration in the damaged tubule.

The sections taken from the hemorrhagic areas in the liver demonstrated moderate changes. The general architecture of this portion was obscured because of recent hemorrhage into the liver with necrosis of the hepatic cells. The sinusoids were considerably congested. In these areas some of the hepatic cells had lost the cellular outline, while others had but a thin granular eosinophilic network with pyknotic or absent nuclei. There was moderate fibrous infiltration

into the periportal areas. The sections taken from other areas in the liver revealed but minimal degeneration, with the same moderate fibrosis throughout the liver in the periportal areas and with some regeneration of bile ducts. A sudan III stain of the liver demonstrated no fatty change, but a Maasson trichrome stain showed the collagenous fibrosis of the periportal areas.

There were no other contributory conditions observed and permission for the examination of the brain and spinal cord was denied.

Anatomic Diagnosis: (1) Rheumatic heart disease with mitral and tricuspid stenosis; (2) chronic passive congestion in the liver, spleen, pancreas, kidney; (3) poisoning due to mercurophylline; (4) nephrosis, toxic, of the kidney;

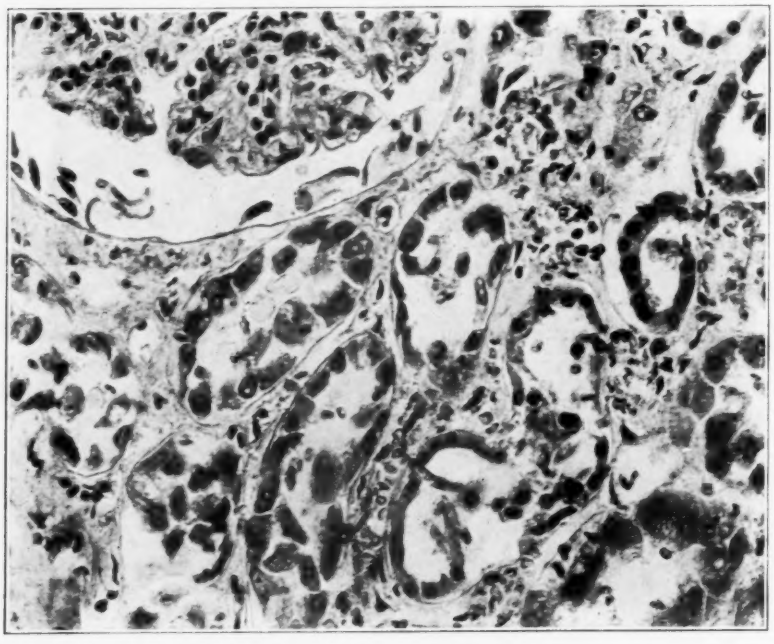

Fig. 2.—This shows the regeneration of tubules with low cuboidal epithelium and hyperchromic elongated nuclei. A mitotic figure may be seen near the center of the photograph (× approximately 368).

(5) necrosis, toxic, of the liver; (6) hemorrhage in the ileum and colon, and (7) bronchopneumonia—terminal were diagnosed.

Qualitative Chemical Analysis: On 10 Gm. of tissue the Reinsch test and the confirmatory Gettler test for mercury were performed, and mercury was demonstrated to be present in the kidney.[6] On 20 Gm. of liver similar tests were performed which elicited faintly postive reactions for mercury.

6. Simmons, J. S., and Gentzkow, C. L.: Laboratory Methods of the United States Army, ed. 5, Philadelphia, Lea & Febiger, 1944, pp. 335-336.

COMMENT

It appears certain that mercurophylline was responsible for the outcome in this case. The presence of mercury at the site of damage in the kidneys and liver was demonstrated by chemical analysis. This factor, plus the characteristic pathologic evidences of tubular necrosis and hemorrhage in the ileum and colon, substantiates mercury as the causative agent. Although there was no calcification in the tubules, this does not eliminate mercury as the cause of the nephrosis, as calcification does not occur in many of the kidneys damaged by mercuric chloride. Regeneration of tubules with hyperchromic nuclei and poorly staining cytoplasm, with an occasional mitotic figure, is not uncommon in diffuse kidney disease and has been seen after the experimental use of mercury to induce nephrosis.[7] Therefore, mercurophylline in this case has produced a pathologic picture similar to that of poisoning by mercuric chloride.

The damage to the hepatic cells may possibly result from extreme passive congestion, but because of the severity of the process, the presence of mercury in the liver and the characteristic finding of mercuric poisoning in the other organs, it seems likely that mercury was responsible for this damage.

The problem of treatment in a case of anuria is still unsettled. Large amounts of fluid are usually administered, although there is some evidence that restriction of fluid intake and bilateral renal decapsulation may be of value. This issue has been recently reopened by Peters,[8] who believes that an increase in intrarenal pressure is the factor which inhibits the flow of urine and not tubular blockage by detached necrotic cells or low arterial blood pressure. This patient was temporarily benefited by renal decapsulation. But until the mechanism of anuria is more clearly understood there will be evidence for and advocates of both methods of treatment.

The undesirable and even fatal effects which occasionally follow use of mercurial diuretics are well known, and the physician naturally takes precautions to minimize the hazards, particularly those which seem due to acquired sensitivity. These agents are, unfortunately, the most effective means now available to remove salt and water from patients in whom these substances are excessively retained, and their use will be widespread and in some cases continuous over many years. One patient[9] has taken as much as 1,250 cc. in 627 injections, and

7. Oliver, J.: Histogenesis of Chronic Uranium Nephritis, J. Exper. Med. **21**:425, 1915.

8. Peters, J. T.: Oliguria and Anuria Due to Increased Intrarenal Pressure, Ann. Int. Med. **23**:221 (Aug.) 1945.

9. Friedenson, M.: The Prolonged Use of Mercurial Diuretics in Heart Failure, Ann. Int. Med. **20**:306 (Feb.) 1944.

others have taken hundreds of injections with only beneficial results. Until patients can be given satisfying sodium-free diets, or until better agents are developed for removing retained sodium, physicians will continue to use the mercurial diuretics.

SUMMARY

A case is reported of a 35 year old woman with rheumatic heart disease and cardiac decompensation, who received mercurophylline parenterally for six months, and who developed an acute anuria, fatal in spite of bilateral decapsulation of the kidney. Postmortem examination revealed nephrosis, hemorrhage in the ileum and colon and focal areas of necrosis and hemorrhage in the liver. Mercury was found in the liver and kidney. The death was attributed to mercurial intoxication.

Note.—Since this article was submitted for publication a similar case of toxic nephrosis due to mercurophylline has been the subject of a clinicopathologic case report (Cabot Case 31451, New England J. Med. **233**:567 [Nov. 8] 1945).

2213 Callow Avenue, Baltimore 17.

INFECTIOUS MONONUCLEOSIS

A Consideration of the Complications and a Preliminary Report on the Use of Penicillin in This Disease

MAJOR FRANK T. JOYCE
MEDICAL CORPS, ARMY OF THE UNITED STATES

RENEWED interest in the diagnosis of infectious mononucleosis has developed since the introduction of the Paul-Bunnell test in 1932.[1] Although a positive heterophile antibody reaction is not essential in making the diagnosis of this disease, the reaction is almost pathognomonic when positive. The early or frequent use of this test may establish a diagnosis when the clinical signs are confusing or before suggestive or diagnostic changes in the white blood cells have occurred; however, it may not be positive during the acute phase of the disease, nor is it necessarily related to the changes in the blood picture. Blood smears and Paul-Bunnell tests may have to be repeated several times before the diagnosis is established. Usually these procedures are not frequently repeated in the management of private patients because of the expense involved. This becomes even more apparent should the patient have a mild form of the disease. It seems probable, therefore, that many cases of infectious mononucleosis are incorrectly diagnosed as influenza, tonsillitis, sore throat, Vincent's angina or some other benign disease.

Epidemics of infectious mononucleosis have been reported; in 1943 an account of an epidemic in an Emergency Medical Service hospital in Scotland was reported by Halcrow, Owen and Rodger [2] in which 290 cases of infectious mononucleosis were detected. In 125 of these the patients were ill enough to have clinical symptoms, but in 165 cases the patients had a subclinical form of the disease, which was discovered only by doing blood smears and establishing the presence of a positive heterophile antibody reaction. This is surprising when one considers that 57 per cent of these patients were not clinically ill. Press, Shlevin and Rosen [3] listed 36 presenting symptoms in their series of cases. Text-

Read before the Army Air Forces South Central Medical Conference, San Antonio, Texas, May 3, 1945.

1. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90-104 (Jan.) 1932.

2. Halcrow, J. P. A.; Owen, L. M., and Rodger, N. O.: Infectious Mononucleosis with an Account of an Epidemic in an E.M.S. Hospital, Brit. M. J. **2**:443-447 (Oct. 9) 1943.

3. Press, J. H.; Shlevin, E. L., and Rosen, A. P.: Infectious Mononucleosis: A Study of Ninety-Six Cases, Ann. Int. Med. **22**:546-562 (April) 1945.

books and medical journals mention the milder forms of the disease, but the usual description includes headache, malaise, fever, sore throat, enlarged spleen and lymph nodes, with possibly a rash, meningeal signs or jaundice, accompanied with changes in the white blood cell elements and a positive reaction to the Paul-Bunnell test. Evidence is now accumulating which indicates that this clinical picture represents the severer form of the disease.

An infectious disease which shows such a wide range in severity and which may present a great variety of symptoms is often difficult to diagnose. Benign as it is, it is set apart from the usual infectious or contagious disease when one is confronted with an acutely ill patient concerning whom observations are confusing and laboratory reports do not reveal any abnormalities. The severity of the acute phase in some cases often leads one to abandon the diagnosis of infectious mononucleosis if there is no suggestive or confirmatory support from the laboratory. Later, as the patient improves, the diagnosis becomes established. From time to time authors [4] on this subject have separated cases of infectious mononucleosis into types according to the predominant symptoms and physical observations. These classifications of the disease reflect its protean nature. In such an infectious disease it is sometimes difficult to decide which symptoms are part of the disease and which may be arising from the complications which occur.

Ulcerative pharyngitis and tonsillitis occurring in infectious mononucleosis have been described so frequently that these conditions have come to be regarded by many as a symptom of the disease. Sore throat is undoubtedly one of the commonest symptoms, and many patients have it in some degree sometime in the course of their illness. Contratto [5] stated that sore throat was present in 82 per cent of 196 cases; and Press, Shlevin and Rosen [3] reported sore throat in 68.7 per cent of 96 cases. However, in both of these large series of cases the occurrence of ulcerative pharyngitis and tonsillitis was relatively low–22 per cent in Contratto's cases. In the series of cases reported by Press and his colleagues, the incidence of tonsillitis was not given, but they did not observe a single case of ulcerative pharyngitis or Vincent's stomatitis. Halcrow and his colleagues [2] found sore throat in 35 of the 125 patients who were clinically ill, but only 4 had the "anginose" type. Read and Helwig,[6] in

4. (*a*) Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1944, p. 464. (*b*) Walker, W. H.: Infectious Mononucleosis, Bull. U. S. Army M. Dept., December 1944, no. 83, pp. 80-93.

5. Contratto, A. W.: Infectious Mononucleosis: A Study of One Hundred and Ninety-Six Cases, Arch. Int. Med. **73**:449-459 (June) 1944.

6. Read, J. T., and Helwig, F. C.: Infectious Mononucleosis: An Analysis of Three Hundred Cases with Three Characterized by Rare Hematologic Features Arch. Int. Med. **75**:376-380 (June) 1945.

an analysis of 300 cases, reported 150 (50 per cent) cases of the anginose type, but membranous pharyngitis occurred in only 34 cases (11 per cent), and acute tonsillitis occurred in only 29 cases (10 per cent). The combined cases were 21 per cent. Although sore throat is part of the disease, ulcerative pharyngitis, follicular or ulcerative tonsillitis and Vincent's stomatitis should be regarded as complications. In most cases specific virulent organisms are present, such as streptococci, pneumococci, fusiform bacilli and spirochetes. When these complications occur as the presenting symptoms they often mask any other complaints. When occurring after the diagnosis of infectious mononucleosis has been established, they are frequently more disabling than the disease itself, even though the acute phase may have been quite severe.

Since the origin of infectious mononucleosis is unknown, no specific therapy has been developed. A virus is suspected,[7] but the disease has not been consistently reproduced in man or in laboratory animals. Assuming that the causative agent is a virus, it would not be expected that sulfonamide therapy or penicillin would be of benefit. One case of infectious mononucleosis was reported [8] to have developed in a patient who was undergoing an intensive course of penicillin therapy while being treated for osteomyelitis. Recently, authors [9] of papers on penicillin have listed infectious mononucleosis as one of the diseases in which penicillin should not be used. This attitude regarding the use of penicillin in infectious mononucleosis is logical, but unfortunately it has been too closely followed, with the result that penicillin is not being used in any phase of the disease. The commonest and also one of the severest complications seen in infectious mononucleosis is sore throat or tonsillitis which is caused by the invasion of the host by well known organisms, and it is expected that penicillin, and to a much smaller extent, sulfonamide drugs, would be of considerable value in these conditions. Penicillin and sulfadiazine were used in the treatment of some of our patients. Although the number of patients treated with penicillin are few, there was only 1 who did not respond dramatically when penicillin was used in infectious mononucleosis to treat those complications which are frequently considered a part of the disease per se.

The incidence of sporadic cases of infectious mononucleosis is higher than would be expected when compared to other well known diseases

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7. Julianelle, L. A.; Bierbaum, O. S., and Moore, C. V.: Studies on Infectious Mononucleosis, Ann. Int. Med. **20**:281-292 (Feb.) 1944.

8. Bloomfield, A. L.; Kirby, W. M. M., and Armstrong, C. D.: A Study of "Penicillin Failures," J. A. M. A. **126**:685-691 (Nov. 11) 1944.

9. Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with Analysis of One Hundred and Fifty Cases in Which It Was Employed, J. A. M. A. **125**:1003-1010 (Aug. 26) 1944. Bloomfield, Kirby and Armstrong.[8]

affecting the same age group. It is probable that there have been cases of infectious mononucleosis misdiagnosed because it too closely resembled some other disease, and with this thought in mind the histories of all cases of acute follicular and ulcerative tonsillitis, Vincent's angina and infectious hepatitis occurring in 10,000 consecutive hospital admissions were reviewed to determine whether those particular records contained clinical or laboratory evidence suggestive of infectious mononucleosis. There were among those 10,000 cases 31 sporadic cases of infectious mononucleosis, 25 cases of infectious hepatitis, 51 cases of Vincent's angina and 307 cases of acute tonsillitis.

ACUTE FOLLICULAR OR ULCERATIVE TONSILLITIS

There were 307 admissions with a diagnosis of acute follicular or ulcerative tonsillitis, but white blood cell counts were done in only 175 cases, and only those cases were considered. Among the 175 cases of tonsillitis there were 15 cases in which the differential white blood cell count revealed either a moderate or pronounced preponderance of the monocytic series; a specific mention was made of the presence of abnormal lymphocytes, or the total white blood cell count (disregarding the differential count) was less than 9,000 in the presence of a temperature higher than 102 F. (38.9 C.). In the latter group of cases the temperature was more often 103 F. (39.4 C.) or higher. In not one of these cases was infectious mononucleosis suspected, and Paul-Bunnell tests were not made during the time the patients were hospitalized; however, 1 patient, whose case is not included among the 15, was readmitted to the hospital one week later with generalized enlargement of the lymph nodes, and the reaction to the Paul-Bunnell test was positive in a 1 : 160 dilution on admission. The blood counts or the clinical course during his tonsillitis did not reveal anything suggestive of infectious mononucleosis, as shown by his chart; this leads one to wonder what more suggestive evidence of infectious mononucleosis need be present besides the suspicion.

Throat smears or throat cultures were done in 77 cases. The majority, 45, contained nonhemolytic streptococci. There were 9 in which Vincent's organisms were present but not thought to be the causative agent, and in the remainder no pathogenic organisms were found.

VINCENT'S ANGINA

Among the 10,000 cases there were 52 cases of Vincent's angina. It is generally accepted that the symbiotic organisms Borrelia vincenti and Fusobacterium plauti-vincenti may be found in the mouths of apparently healthy persons, and no discussion as to their pathogenicity will be made; suffice it to say that the diagnosis of this disease was made in conformity with generally accepted principles. These cases were likewise studied in search for evidence suggestive of infectious mononucleosis.

When applicable the same factors were considered. In almost all of the cases there was either a membranous pharyngitis or tonsillitis. Of the 52 cases white blood cell counts were not done in the first 19 because of inadequate laboratory facilities. Of the 33 remaining cases, in which total and differential white blood cell counts were done, there were only 2 cases suggestive of infectious mononucleosis. This incidence was surprisingly low. In both cases Paul-Bunnell tests were done, one before the patient's discharge from the hospital and the other eight days following the patient's discharge. In both cases reactions to the Paul-Bunnell tests were negative. In many of the cases there were enlarged cervical lymph nodes, but there was no mention of enlarged nodes elsewhere. In only 39 cases were throat smears done, and 35 of those were found to have reactions of 2 to 4 plus (on an arbitrary scale) for Vincent's organisms.

The most striking feature revealed in a review of the cases of Vincent's angina was the fact that, although a membrane was present in most cases and although the patients were ill enough to be hospitalized for an average of eleven days per patient, they seldom had a temperature of over 100.4 F. (38 C.). This absence of a high temperature in such cases is in sharp contrast to those cases in which Vincent's angina exists as a complication of infectious mononucleosis, in which the temperature is often much higher. In 43 of the 52 cases there was a temperature of less than 100 F. (37.8 C.).

INFECTIOUS HEPATITIS

This disease was considered because jaundice is occasionally present in infectious mononucleosis. Its frequency of occurrence is low. Caution was used in evaluating the significance of low white blood cell counts or the ratio of neutrophils and monocytes. Similar abnormalities in the blood may be present in infectious hepatitis and early in infectious mononucleosis. There were 25 cases of infectious hepatitis. There were 4 cases in which the observations were suggestive of infectious mononucleosis. In 1 of the 4 cases there was a total white blood cell count of 4,600, with 41 per cent neutrophils and 59 per cent cells of the monocytic series. The temperature of the patient was 102.4 F. (39 C.) on admission and remained above 101 F. (38.3 C.) for three days. Infectious mononucleosis was considered, but only one Paul-Bunnell test was done, and the reaction to it was negative. In 1 case the maximum white blood cell count was never over 4,000, with 44 per cent neutrophils and 56 per cent cells of the monocytic series. In this case the fever was 103.4 F. (39.6 C.), and an eruption was present for two days. Unfortunately, a test for the presence of heterophile antibodies was not done. Another case was even more striking; there was a white blood cell count of 10,750, with only 8 per cent neutrophils and with the remainder, 92 per cent, of the monocytic series.

INFECTIOUS MONONUCLEOSIS

The diagnosis of infectious mononucleosis was confirmed in all but 1 case by a positive reaction to the Paul-Bunnell test with a dilution of 1 : 40 or higher. Most often no further determinations were done after the first positive reaction was obtained. In any event the diagnostic criteria mentioned by Kaufman [10] were present in each case.

There were 31 sporadic cases of infectious mononucleosis occurring in 10,000 consecutive hospital admissions. There was no recognized epidemic. These cases occurred within a period of twenty-three months. In the later months the medical staff became more interested in infectious mononucleosis, which resulted in more diagnoses being made and confirmed. In the first month after the case study was completed there were 6 cases diagnosed. This emphasizes the importance of looking for infectious mononucleosis in any ill defined infectious disease. This diagnosis was made in only 6 of the 31 cases at the time of admission. The duration of the disease at the time of admission varied from one to nine days, the average being four days. The onset of the complication ranged from one to sixteen days, the average being seven days. The number of days in the hospital for all patients varied from six to thirty-six, with an average of twenty; however, these patients were not released from the hospital until each was capable of performing full duty.

The clinical course varied. In 11 cases the highest temperature did not exceed 101 F. (38.3 C.), and neither tonsillitis nor membranous pharyngitis was present. In 12 of the 31 cases the temperature exceeded 104 F. (40 C.) and was of the daily remitting type accompanied by chills. Until the diagnosis was made, malaria, septicemia or diphtheria was often suspected. In arriving at the diagnosis in such cases, before the blood counts become suggestive of infectious mononucleosis or the reaction to the Paul-Bunnell test becomes positive, one is apt to look with doubt on the frequently written statement that this disease is benign.

The frequency and type of complication are of no statistical significance in this small group of cases but will be included for the sake of completeness. In 11 cases there was no complication. There was 1 case of otitis media and 1 case of albuminuria. Acute tonsillitis was present in 11 cases and ulcerative pharyngitis was present in 8 cases. Throat smears or cultures contained Vincent's organisms in 10 cases, hemolytic streptococci in 3 cases, and nonhemolytic streptococci in 2 cases.

No new information was learned from studying the white blood cell counts or the differential counts in relation to the onset of the complication, the height of the fever or the appearance of a positive reaction for

10. Kaufman, R. E.: Heterophile Antibody Reaction in Infectious Mononucleosis, Ann. Int. Med. **21**:230-251 (Aug.) 1944.

heterophile antibodies. No consistent correlation of these factors was present.

TREATMENT OF COMPLICATIONS

Sulfadiazine was used in many cases of sore throat and tonsillitis complicating infectious mononucleosis, but only those which received this form of medication in the usual dosages for at least two days were considered as having been adequately treated. There were 8 such patients. The response of 3 patients to sulfadiazine was considered good and for the remainder the results were equivocal. Of the last 7 patients of the series there were 4 sufficiently ill with ulcerative pharyngitis or tonsillitis and high fever to warrant the trial of penicillin. Three of the 4 patients had ulcerative pharyngitis, while the other had tonsillitis. These complications occurred nine, sixteen, eight and two days, respectively, after the onset of the disease. Vincent's infection was present in only 1 of the patients. Each of the patients had considerable involvement, complained bitterly of pain, and had a temperature from 102 F. to 104 F. (38.9 C. to 40 C.). For 3 of the 4 patients there was a dramatic improvement in the symptoms and appearance of the throat as well as a fall in temperature within twelve to twenty-four hours. The doses were 20,000 Oxford units given intramuscularly every three hours with an ice bag placed over the site of injection. The total dosages were from 160,000 to 460,000 units. In the patient who did not seem to respond so favorably the pharyngeal ulcers began to heal, but there was slow progress, and the temperature of 103.6 F. (39.7 C.) gradually subsided within three days. The throat culture revealed nonhemolytic streptococcus, and the smear was 4 plus positive for Vincent's organisms.

REPORT OF CASES

CASE 1.—A white officer, 24 years old, was admitted to the hospital March 2, 1945, complaining of chills, fever, malaise and headaches which had begun approximately five days before admission. The chills and fever occurred on February 26 and 28 and March 1, 1945. During the intervals between chills he felt fairly well and did not report for medical treatment. There had been no nausea, vomiting, diarrhea or abdominal pain, and he did not have a cough, sore throat or other symptoms of respiratory infection. The patient stated that he had been in Hawaii for a few days in October 1942 and had completed approximately one year of service in England about one year previously, returning to the United States in January 1944. He gave no history of having been exposed to infectious or contagious diseases. The past and familial history was irrelevant. This patient had had thirty-two months of duty on flying status and had been in good health except for minor respiratory infections.

The temperature on admission was 101.8 F. (38.7 C.). The skin was dry and he appeared to be acutely ill. The nose and throat were normal. He had considerable headache but there was no rigidity of the neck. No lymph nodes were palpable. There were no rales or dull areas in the lungs. The blood pressure was 115 systolic and 70 diastolic. The pulse was 112 and regular in rhythm.

The heart was not enlarged, there were no murmurs and the heart sounds were of good quality. Examination of the abdomen revealed the spleen to be barely palpable and tender. The liver was neither palpable nor tender. There was an appendectomy scar. The remainder of the examination of the abdomen revealed nothing abnormal. The superficial and deep reflexes were all normal.

For four days following admission, the patient had daily chills with temperature spiking to 104 F. or 105 F. (40 C. to 40.6 C.). Because of the enlarged, tender spleen and the lack of other signs, a tentative diagnosis of malaria was made on the second hospital day. The white blood cell count on admission was 6,400, with 72 per cent neutrophils and 28 per cent lymphocytes; there was no significant change during the first five days. Specimens of urine were normal. Thick and thin blood smears were repeatedly found negative for malarial parasites. However, in spite of the negative blood smears, 3 grains (0.2 Gm.) of quinacrine hydrochloride was given every six hours for five doses, starting on the second hospital day. The chills and high fever subsided on the fourth day, but a temperature of 101 F. to 102 F. (38.3 C. to 38.9 C.) persisted for three days. On the fifth

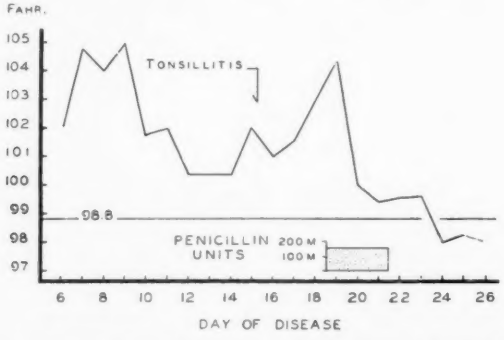


Fig. 1 (case 1).—The secondary rise of temperature is associated with the development of severe tonsillitis occurring in infectious mononucleosis, the so-called anginose type. The dramatic response to penicillin is illustrated by the abrupt drop in the temperature curve.

day small nontender lymph nodes were felt in the left posterior cervical triangle. The following day the spleen became definitely larger, and the diagnosis was changed to infectious mononucleosis, and quinacrine was discontinued. During this time there had been very little change in the white blood counts except for a slight increase in lymphocytes up to 45 per cent, with the total white blood cell count not exceeding 7,300. The Paul-Bunnell test elicited a negative reaction, and examination did not reveal abnormal lymphocytes in the blood smears. The Weil-Felix reaction was negative. On the seventh hospital day the temperature fell to not more than 100 F. (37.8 C.) and the patient seemed to be over his disease. However, on the eleventh hospital day he began to complain of sore throat, the temperature began to rise, and a repeat white blood cell count was 21,050, with 57 per cent lymphocytes, 4 per cent monocytes and 39 per cent neutrophils. Prior to this time the heterophile antibody reaction had remained negative, but a repeat test done on that day was positive, in a 1:320 dilution. The sore throat became progressively severer. Both tonsils enlarged rapidly and were covered with a gray pseudomembrane. A smear for Vincent's organisms was negative. He

complained bitterly of extremely sore throat, and swallowing or talking was very difficult. The temperature gradually rose so that on the third day following the onset of the tonsillitis, it had reached 104 F. (40 C.). At this time 20,000 Oxford units of penicillin were given intramuscularly every three hours. Within twelve hours the throat appeared much better, and the patient did not complain of so much pain. The temperature fell by crisis and in less than twenty-four hours it was not above 100 F. (37.8 C.). The throat very rapidly improved so that within three days it appeared normal. Penicillin was continued in treating the tonsillitis for three days for a total of 460,000 units. The patient's convalescence was slow. He was discharged to full duty thirty-two days after his admission.

CASE 2.—A white officer, 24 years old, was admitted on March 13, 1945, complaining of enlarged lymph nodes in the left side of his neck which had been present for five days. On admission this patient did not appear ill, but a heterophile antibody test done the day prior to admission elicited a positive reaction in a dilution of 1 : 320. The white blood cell count was 6,850, with 36 per cent

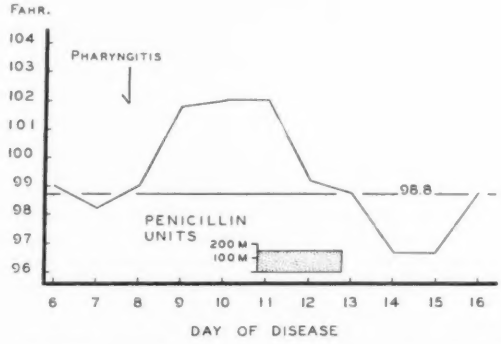


Fig. 2 (case 2).—The onset is illustrative of a severe ulcerative pharyngitis as a complication of infectious mononucleosis (anginose type) and the response to penicillin.

neutrophils and 64 per cent lymphocytes. The blood smear revealed abnormal lymphocytes. The physical examination showed nothing abnormal except for slightly enlarged lymph nodes in the submental area and in the left anterior cervical region. The spleen was not palpable. The patient did not complain of sore throat, and the throat appeared normal on examination. However, on the second hospital day he complained of sore throat, but there was no enlargement of the tonsils. By the third day the temperature had reached 101.4 F. (38.5 C.), and the sore throat had become much worse. Examination revealed an ulcerative pharyngitis. In the meantime the lymph nodes of the neck became considerably larger, and there was slight enlargement of the axillary lymph nodes. On the fifth hospital day, which was the tenth day of his illness, the temperature was elevated to 102 F. (38.9 C.), and the patient was acutely ill. Twenty thousand units of penicillin were given every three hours intramuscularly for a total of 320,000 units. The temperature very promptly subsided and within twelve hours had fallen to normal, with noticeable improvement in the throat. The subjective improvement in the throat was more pronounced than the physical appearance,

but the pharyngitis rapidly subsided and the patient made an uneventful recovery. He was discharged from the hospital fourteen days after admission.

CASE 3.—An officer, 24 years old, was admitted to the hospital on April 3, 1945, on the third day of his illness. The onset was accompanied by chills, fever, malaise and generalized aching pains. He also noticed soreness and bleeding of the gums, and the following day he reported to the dental clinic, where a diagnosis of Vincent's gingivitis was made, and penicillin mouth washes were prescribed. On the third day he awakened with high fever, all his symptoms had become worse, and he had a very sore throat. The past personal and familial history was irrelevant.

On admission his temperature was 103 F. (39.4 C.). He appeared very ill, and talking and swallowing were painful. Both gums were swollen, bled easily on touching and showed numerous small white ulcers. The tonsils had been enucleated but the tonsillar fossae were studded with lesions similar to those on the gums. The pharynx was acutely inflamed but showed no ulceration. The ears, eyes and nose were normal. The lymph nodes in both anterior cervical triangles were enlarged and were slightly tender. The lungs were normal. The cardiovascular system was normal; the pulse rate was 110, and the blood pressure was 115 systolic and 60 diastolic. There was no tenderness or enlargement of the abdominal viscera on palpation. The urogenital organs were normal. Except in the neck, the lymph nodes were not enlarged enough to be felt. Ninety grains (6 Gm.) of sulfadiazine with 180 grains (12 Gm.) of sodium bicarbonate were given during the first eight hours, followed by 15 grains (1 Gm.) of sulfadiazine and 37.5 grains (2.5 Gm.) of sodium bicarbonate every four hours. The penicillin mouth washes which had been started on the day prior to admission were continued. Although the diagnosis of Vincent's infection had already been made, a throat culture revealed nonhemolytic streptococci and pneumococci as the predominating organisms. No diphtheria bacilli were seen on smear or grown on culture. The white blood cell count was 10,700, with 67 per cent neutrophils, 31 per cent lymphocytes and 2 per cent eosinophils. No abnormal lymphocytes were seen. The urine, hemoglobin and red blood cell count were normal.

The day after admission the temperature was 103.4 F. (39.6 C.), and the throat and mouth lesions were worse. Use of sulfadiazine was stopped and penicillin begun, 20,000 units intramuscularly every three hours. The white blood cell count had dropped to 6,500, with 80 per cent neutrophils and 20 per cent lymphocytes. The heterophile antibody reaction was negative. The temperature remained elevated during the first twenty-four hours after the penicillin was begun and, although the patient complained less of the sore throat, there was no apparent change in the appearance of the gums or throat. Penicillin was continued, and after forty-eight hours the temperature had dropped to 100.4 F. (38 C.), with considerable improvement in the appearance of the throat lesions but with no noticeable change in the gums. Penicillin intramuscularly was continued until he had had 460,000 units over a period of sixty-nine hours. At the end of this time the temperature ranged from 98.6 F. to 100 F. (37 C. to 37.8 C.). The white blood cell count was 6,750, with 52 per cent neutrophils, 6 per cent eosinophils and 42 per cent lymphocytes. Although infectious mononucleosis had been suspected, this slight increase in the lymphocytes was the first laboratory evidence suggestive of this diagnosis. Four days later (the eighth hospital day) the heterophile antibody reaction became positive in a dilution of 1:80, and six days later it became negative. There were no diagnostic observations of the blood picture during the short time the heterophile antibody test elicited a positive reaction.

However, after the reaction had become negative, the blood picture became typical of infectious mononucleosis.

The gingivitis continued to cause trouble for six days after the course of penicillin had been completed, in spite of the continuous use of the penicillin mouth washes. Although there had been healing of the ulcers, the gums remained edematous, bled easily and healed slowly. The patient had no fever during this time. At no time did lymph nodes become palpable except in the neck, and the spleen was never felt. He returned to duty fifteen days after admission.

COMMENT

During World War II, military medicine afforded opportunity for one to determine effectively the incidence of diseases which are peculiar to the group of military age. In this respect (excluding battle casualties) military hospitals would compare with infirmaries serving college students, since the age groups are approximately the same. Contratto [5] reports that infectious mononucleosis accounted for 1.5 per cent of 12,601 medical admissions. In this study infectious mononucleosis was present in 0.31 per cent of 10,000 patients admitted consecutively to the medical and surgical services. There was an insignificant number of battle casualties among those admitted to the surgical services. The ratio of the patients admitted to the medical services and those to the surgical was not actually determined, but 10 samples of 100 patients each, spread equally over a twenty-four-month period, showed the proportion to be 72 per cent admitted to the medical and 28 per cent to the surgical services. The corrected incidence of infectious mononucleosis was 0.43 per cent of 10,000 patients admitted to the medical services. This is considerably lower than the incidence given by Contratto, and although military hospitals are occupied almost exclusively by males, a correction for the sex ratio would still not elevate the percentage more than twofold. As was brought out by Contratto, the percentage of patients admitted for infectious mononucleosis in a hospital concerned chiefly with the treatment of young adults is much higher than in a general hospital, which cares for patients of all ages. He reported 61 patients with infectious mononucleosis among 16,907 patients admitted to the medical services of Peter Bent Brigham Hospital in a period of seven years and nine months.

The pseudomembrane covering the ulcerative pharyngeal or tonsillar lesions in infectious mononucleosis is sometimes mistaken for diphtheria. When it is present the throat smears are often positive for Vincent's organisms. It is not uncommonly seen in infectious mononucleosis, and almost every report on the clinical aspect of this disease contains some reference to it. The report of Press and his colleagues [8] is unique in this respect, since they state that they did not observe a single case of Vincent's angina in their large series of cases of infectious mononucleosis. In this series of cases, Vincent's organisms were present in 10 (52

per cent) of the 19 cases of infectious mononucleosis which were complicated by pharyngeal or tonsillar lesions. Considering this relatively high incidence of Vincent's angina as a complication of infectious mononucleosis, it was expected that a review of the case histories of primary Vincent's angina would reveal a high incidence of cases containing evidence that infectious mononucleosis may have been the proper diagnosis. This did not prove to be true. Only 2 such cases were found among the 33 cases of Vincent's angina which were considered in this study. This amounted to 6 per cent and was lower than the anticipated level. Eight per cent of the clinical records of 175 cases of acute tonsillitis revealed considerable evidence that infectious mononucleosis should have been the proper diagnosis. Eight per cent of the cases of infectious hepatitis contained similar evidence suggestive of an improper diagnosis. Many reports on infectious mononucleosis mention how frequently this disease may be missed because it may simulate these conditions. To my knowledge, these are the first statistical studies in this respect, and serve only to emphasize what has been long known but too frequently forgotten.

Sore throat is so frequently seen in infectious mononucleosis that in the absence of acute ulcerative pharyngitis or acute tonsillitis, it must be considered as one of the symptoms of infectious mononucleosis. The cause is obscure and without visible local pathologic conditions it is not possible to say that this is due to secondary infection. Ulcerative pharyngitis and acute tonsillitis do not fall in this same category. It is easy to incriminate the tonsillar lesions as being part of the disease entity when the lymph nodes throughout the body may be generally involved. However, the ulcerative lesions may occur on the soft palate, the tonsillar pillars or the posterior pharyngeal wall and often do not arise from involved lymphoid tissue. Bernstein,[11] in his excellent review, stated his belief that ulcerative pharyngitis and acute tonsillitis were complications rather than part of the disease itself, and that these inflammatory lesions are not different from similar complications occurring in such conditions as the leukemias or agranulocytosis.

Why these two particular complications should occur so frequently in infectious mononucleosis has not been determined. Undoubtedly, there must be a lowered resistance of the patient to virulent organisms. There seems to be little relation between the onset of these complications and the white blood cell count. In some cases showing severe throat lesions the neutrophile count may be low, normal or elevated. A relative or absolute lymphocytosis with a corresponding granulocytopenia usually occurs at some time in infectious mononucleosis, and it would seem that the granulocytopenia might be responsible for the lowered resistance of the host. While this may be true in some cases, granu-

11. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85-159 (Feb.) 1940.

locytopenia frequently does not occur until perhaps long after the throat complication has subsided. Read and Helwig [6] believe that granulocytopenia, anemia, or thrombopenia occurring in infectious mononucleosis is the result of a focal infectious granulomatous process in the bone marrow with a secondary depression of hemopoietic activity. Others regard this pathologic process as a simple heteroplastic infiltration of the bone marrow. In either case, the absence of leukocytosis in the tonsillitis or membranous pharyngitis complicating infectious mononucleosis might well be accounted for by an inability of the hemopoietic system to respond rather than by a lack of stimulation and would not, therefore, be a valid argument that these particular throat lesions are part of the disease entity. Menkin [12] has reported a substance found in inflammatory exudates and hemolyzed blood serum which he has called necrosin. When necrosin is injected into test animals, an inflammatory reaction occurs at the site of injection which is accompanied by systemic changes manifested by high fever, diarrhea, damage to the liver and granulocytopenia. Although a granulocytopenia does not always occur in infectious mononucleosis, it is possible that necrosin or some similar substance is liberated which suppresses the normal neutrophile response to a secondary invasion of the host. In general, however, virus infections (and some bacillary infections) cause very little neutrophile response, and ulcerative pharyngitis or tonsillitis is a not frequently occurring complication of such diseases.

The throat lesions complicating infectious mononucleosis were found to occur on an average of seven days after the onset of the disease. Almost invariably these lesions were accompanied with fever, which in some cases was high. In many of the cases the fever was low during the first few days following admission and became elevated if a throat complication developed. In other cases the initial phase of the disease may have been very stormy and the patient might have chills and high fever for two or more days; this would subside with apparent recovery from the disease for a few days. However, after this brief interlude of well-being the throat complications developed and were accompanied with another rise in fever, which in some cases was higher than the fever occurring during the initial phase of the disease. When this occurred, the patient was usually more acutely ill and uncomfortable than during the period of stormy onset. The latter type of fever curve in infectious mononucleosis occurred in 7 of the 31 cases and was similar to the "saddleback" fever which occurs in other diseases. Considerable variation in the degree and type of the fever curve in infectious mononucleosis

12. Menkin, V.: Further Studies on the Leukocytosis-Promoting Factor and on Necrosin in Inflammatory Exudates, Am. J. M. Sc. **208**:290-297 (Sept.) 1944.

has been known for some time. Mills [13] described "saddleback" fever occurring in this disease in 1932. Relapses and recrudescences may occur and could easily explain this type of fever curve, but this clinical feature, which occurred in 23 per cent of this series of cases, has been given very little attention in previous studies of the disease. Contratto mentions this type of fever and states, "The amount of fever and its duration did not seem necessarily related to either the sore throat or the blood count." I agree entirely with that part of the statement in regard to the blood count but in none of the cases in this series in which there was saddleback fever did the secondary elevation of fever occur unless tonsillitis or pharyngitis was present at the same time. Since relapses and recrudescences occur, it would be difficult to prove that the secondary rise in fever was caused by the complicating throat infection. Especially would this seem true when there was no elevation of the white blood cell count.

However, there remains one very strong argument in favor of this contradictory conception, i. e., in 3 of the 4 cases in which penicillin was used to treat the pharyngitis or tonsillitis occurring in infectious mononucleosis there was a dramatic response to this therapy in every respect. While it seems well established that penicillin is of no benefit when used to treat infectious mononucleosis, the only explanation for its dramatic effect in these cases is that it cured a complicating infectious process caused by organisms which are susceptible to penicillin. The 1 exceptional case which did not respond so favorably to penicillin was a case in which there was a very severe Vincent's infection of the gingivae and pharyngeal wall. The temperature in this case fell slowly from 103.2 F. (39.5 C.) to normal within seventy-two hours, and although the patient did feel better, the gingivitis remained troublesome several days after the temperature was normal and in spite of daily penicillin mouth washes. The pharyngeal lesions healed rapidly after penicillin was started. Pearce and McDonald [14] reported the favorable response of fusospirochetosis treated with penicillin. These authors contrasted the results obtained with various dosages. They obtained negative smears in twenty-four hours with complete healing in ninety-six hours in 95 per cent of the cases, using penicillin in doses of 10,000 units every two hours until 100,000 units had been given; these patients also received dental care and oxygenating mouth washes. Not so striking were the results when penicillin was used in the more conventional dosage of 20,000 units every

13. Mills, J.: Glandular Fever, Roy. Berkshire Hosp. Rep., 1932, p. 66; cited by Bernstein.[11]

14. Pearce, W. F., and McDonald, J. B.: Treatment of Ambulatory Patients with Penicillin Sodium: Preliminary Studies of Fusospirochetosis, J. A. M. A. **128**:342-344 (June 2) 1945.

three hours, which was the dosage used in this series of cases. In that group only 53 per cent of the patients were cured in twenty-four hours. The throat smears were negative for Vincent's organisms in the 3 cases in which there was a good response to penicillin.

The response of the throat complications to sulfadiazine when used in adequate doses was considerably less impressive. Fusospirochetosis does not respond well to sulfadiazine, and although streptococcus, staphylococcus, and pneumococcus throat infections respond to the sulfonamide drugs it is seldom that the degree of response is as great as that seen when penicillin is used.

In many patients who are acutely ill with infectious mononucleosis sore throat or tonsillitis never develops. However, the conception that these particular conditions are a part of this clinical entity has become well established, both in regard to the frequency of their occurrence and their causal relationship. Add to this the fact that penicillin is of no benefit in the treatment of infectious mononucleosis per se, and the result will be the failure to use penicillin in the treatment of any phase of the disease. Although the patients treated with penicillin are too few to warrant a dogmatic statement proclaiming its unquestionable value in treating these severe conditions complicating infectious mononucleosis, the results do justify further trial of penicillin in the treatment of infectious mononucleosis, not to treat the disease in all its many forms, but specifically for the throat lesions which not uncommonly are more disabling than any other phase of the disease.

SUMMARY

1. In a study of the case histories of acute tonsillitis, Vincent's angina and infectious hepatitis, evidence was found in 6 to 8 per cent of the cases which indicated that infectious mononucleosis should, perhaps, have been the proper diagnosis.

2. The causal relation of the severe throat conditions in infectious mononucleosis is discussed.

3. Evidence is presented which warrants the further use of penicillin in treating the severe throat lesions accompanying infectious mononucleosis.

NOTE.—After the foregoing paper was accepted for publication French reported a study of 54 cases of infectious mononucleosis (French, P. K.: Infectious Mononucleosis, *Air Surgeon's Bull.* **7:** 414 [Nov.] 1945) and stated that the treatment is purely symptomatic: "Sulfadiazine and penicillin are useful for secondary infections but of no value in mononucleosis itself."

PLASMA QUINACRINE CONCENTRATION AS A FUNCTION OF DOSAGE AND ENVIRONMENT

A Joint Report of the Armored Medical Research Laboratory, Fort Knox, Ky., and the Commission on Tropical Diseases, Army Epidemiological Board, Preventive Medicine Service, Office of The Surgeon General, United States Army

INTRODUCTION

THIS report deals with a study [1] carried out at the Armored Medical Research Laboratory as a part of the program of the Commission on Tropical Diseases of the Surgeon General's Office for the investigation of quinacrine hydrochloride (atabrine) therapy. The primary purposes of the study were: (1) to determine the plasma quinacrine levels in large groups of healthy young men on several suppressive regimens of the drug, (2) to determine the influence of a simulated jungle climate on plasma quinacrine concentrations, (3) to determine the effect of quinacrine on acclimatization and performance of men in humid heat and (4) to determine the plasma concentrations for therapeutic levels of quinacrine intake and relate these concentrations to the plasma concentrations of the same subjects on suppressive regimens. It was anticipated that such information, together with that which was already available,[2] would facilitate the designing of regimens of quinacrine therapy suitable for application to large groups of persons.

The choice of the concentration of quinacrine in the plasma instead of in the whole blood as an index of the effective concentration of the drug has been discussed elsewhere.[2] Briefly the basis is the following: Protein and other cellular constituents have a great affinity for the drug.

The following persons collaborated in this investigation: from the staff of the Armored Medical Research Laboratory—Major Norton Nelson and Lieutenant Colonel Frederick S. Brackett, Sanitary Corps, Army of the United States, and Major William F. Ashe, Major Ludwig W. Eichna and Major William B. Bean, Medical Corps, Army of the United States; specially attached through the Office of the Surgeon General—First Lieutenant E. D. Connor, Lieutenant Colonel A. C. McGuinness, Captain Morris Rosenfeld, Captain L. D. Rosenman and Captain Maurice Wince, Medical Corps, Army of the United States, and Captain R. G. Gould, Sanitary Corps, Army of the United States; representing the Commission on Tropical Diseases, Army Epidemiological Board—James A. Shannon, M.D.

1. Investigation of the Effects of Activity and Environment on Atabrine Therapy, Armored Medical Research Laboratory, Final Report on Project No. 18, Dec. 23, 1943.

2. Shannon, J. A.; Earle, D. P., Jr.; Brodie, B. B.; Taggart, J. V., and Berliner, R. W.: J. Pharmacol. & Exper. Therap. **81**:307, 1944.

In the plasma phase approximately 90 per cent of the quinacrine is reversibly adsorbed by the plasma protein. At normal tissue p_H quinacrine is two to six times as concentrated in red cells as in plasma and one hundred to two hundred times as concentrated in leukocytes as in plasma. Thus, variations in leukocyte count alone may be responsible for large changes in the concentration of quinacrine in whole blood. The most desirable index of the effective concentration of quinacrine would be its concentration in plasma water, since this concentration reflects the distribution of the drug in the various tissues and organs of the body. However, the difficulty of this measurement necessitates the choice, for most purposes, of the total plasma concentration. This can be expected to be a reliable index if the plasma protein concentration is not abnormal and if the distribution ratio from plasma protein to plasma water is stable from time to time and from man to man. The great affinity of protein for quinacrine is perhaps the dominant characteristic in determining the metabolism and distribution of the drug. The body can be considered a quinacrine reservoir of considerable capacity.

Since the plasma quinacrine levels of different men on the same dosage regimen differ widely, it is apparent that the general pattern can be most easily detected and followed in the plasma level of a group. Once the basic characteristics of the pattern are apparent, the extent and frequency of individual deviations from the group pattern can be considered. A second consideration which suggests a useful approach to the analysis of quinacrine metabolism is the characteristic distinction between the changes in plasma level during the twenty-four hours after ingestion of quinacrine and the changes during the days or weeks following a dose. The typical response to ingestion of a single dose of the drug is a rapid rise in plasma quinacrine concentration followed by an initial rapid decrease in concentration which subsequently slows until by twenty to twenty-four hours after ingestion the rate of decrease of plasma quinacrine has decreased to a uniform rate which continues until the plasma is cleared of the drug. The rapid changes in plasma level occurring after ingestion of the quinacrine probably reflect the rapid rate of absorption of the drug and its subsequent distribution throughout the fluids and tissues of the body. The slower changes probably arise from its degradation and excretion. The levels found twenty-four hours after the last dose of the drug, or which would be obtained earlier if absorption and distribution were complete, are considered as "underlying levels"; the concentrations actually determined during the twenty to twenty-four hours after administration are considered as "transient levels," which can be thought of as superimposed on the fictive "underlying level" during this early interval. These concepts have partly dictated the order of presentation of our results, which have been divided into six sections. These are:

I. Plasma quinacrine concentration following single oral doses. This section considers the transient (up to twenty-four hours) changes in plasma quinacrine from a single dose and relates these changes to the previous intake of the drug and to the amount of the dose ingested.

II. Plasma concentrations resulting from several dosage regimens. This section is concerned with the slower trends—over days and weeks—in the plasma quinacrine concentration from several dosage regimens. The gradual build-up of plasma concentration to a steady state, or equilibrium level, is shown for two schedules having a uniform rate of intake throughout. The possibility of more rapidly attaining the desired equilibrium concentrations is considered with respect to three different "booster" or "priming" schedules. Finally, plasma levels are presented for a therapeutic regimen of quinacrine following a suppressive regimen.

III. Plasma concentrations after cessation of dosage and after interruption of dosage. This section considers the rate of disappearance of quinacrine from the plasma when the intake is stopped after attainment of equilibrium concentrations and the rate of increase of plasma concentration after resumption of dosage after interruptions of one week and two weeks.

IV. Individual variation of plasma concentration and prediction of concentration. In this section the spread of individual values within groups on the same schedule are discussed from the point of view of the statistical probability that a given regimen will produce a predetermined concentration of quinacrine in the plasma of a single individual. In addition, a basic generalization is presented which describes the group mean plasma concentration for all the dosage regimens studied.

V. The influence of simulated jungle climate on plasma quinacrine concentration. This section considers whether the plasma quinacrine concentrations in profusely sweating men in humid heat differ from the levels attained by men in a temperate climate and whether intake of the drug modifies the work performance in humid heat.

VI. The toxicity of quinacrine.

PROCEDURE

Chemical Method.—Plasma quinacrine was determined by the method of Brodie and Udenfriend.[3] The method is based on the measurement of the intensity of fluorescence, which, in turn, is proportional to the concentration of quinacrine. Preliminary removal of interfering fluorescent materials is accomplished in two steps: (1) by extraction

3. Brodie, B. B., and Udenfriend, S.: J. Biol. Chem. **151**:299, 1943.

of the organic base, quinacrine, from alkalized plasma by shaking with ethylene chloride (1, 2-dichloroethane) and (2) transfer of the quinacrine from the ethylene chloride to concentrated lactic acid, again by shaking. The fluorescence is measured directly in the lactic acid solution with a photoelectric fluorometer. Minor modifications facilitated the handling of large numbers of specimens.

Preparation of Specimens.—Since the concentration of quinacrine in the leukocytes is very much higher than in the plasma and since leukocytes begin to disintegrate quickly after blood is drawn, it is imperative to separate the plasma soon after drawing the blood in order to avoid contamination of the plasma by quinacrine from the leukocytes. It is necessary to free the plasma of all leukocytes by adequate centrifugation. These conditions can be fulfilled only when the blood stands less than fifteen minutes before centrifugation. Twenty-five to 30 cc. of blood was collected in a 30 cc. syringe containing 6 drops of saturated solution of potassium oxalate. After mixing, the blood was transferred to a tube and centrifugation begun within fifteen minutes of the withdrawal of any blood sample. After centrifugation at 2,000 revolutions per minute for fifteen minutes the plasma was pipetted off and then recentrifuged for an additional hour. This procedure minimized the possibility of accidental contamination by leukocytes.

Reliability of Analytic Results.—It is believed that the management of the bleeding and the preparation of plasma were sufficiently controlled to meet all requirements of the present study. Accidental contamination by leukocytes or extraneous fluorescent materials presented no problem. In several thousand analyses performed there were only 8 or 10 instances in which contamination was demonstrated. A decided advantage was gained by the uniformity of handling which obtains when analyses are carried out on a large scale.

Most of the plasma quinacrine levels encountered were at the lower limits of suitability of the technic. The limiting factors in the procedure are: (1) extraneous nonfluorescent light—this gave deflections equivalent to 8 to 12 micrograms of quinacrine per liter; (2) extraneous fluorescence (irreducible blank in reagents)—amounting to another 8 to 12 micrograms per liter; (3) instrumental limitations, imposed by the sensitivity of the instrument (always used at maximum sensitivity), stability of the instrument, stability of the light source and the residual inequality of the cuvettes. The net effect of these factors was such that the reproducibility of measurement in the range up to 30 micrograms per liter was generally within plus-minus 2 micrograms. The absolute value of the analytic results was generally reliable enough to keep the over-all precision within this range of plus-minus 2 micrograms. In a

few runs the calibration procedure undoubtedly led to considerably greater absolute errors.[4]

Subjects.—The subjects in this study were healthy young adult enlisted men in the army. Their age range was 18 to 37 years with approximately one half between 18 and 20 years, one quarter between 20 and 25 years and one quarter over 25 years. Except for the group living in the humid heat their living conditions, clothing, duties and messing were those of any other soldier. Their medical attention was more solicitious than was that of their confrères in order that toxic manifestations of the drug might not be overlooked. This was done without causing the subjects to focus on their part in the problem. This study was carried out from early August to mid-November 1943.

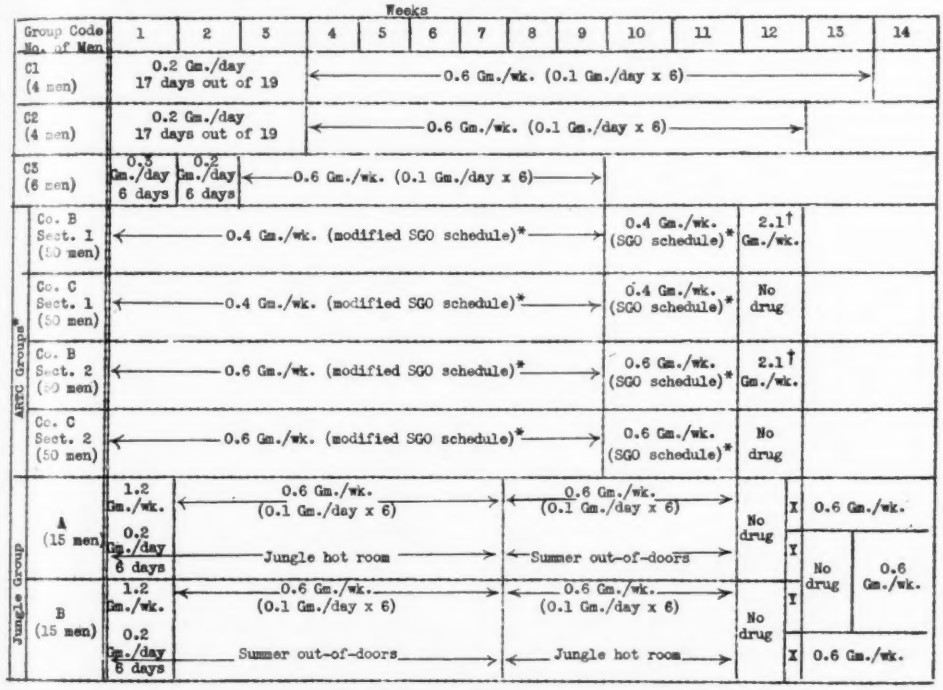
Group Composition.—In order that the various aspects of the metabolism of quinacrine might be studied several groups of men were placed on different dosages and schedules of intake of the drug. Since these groups will be referred to repeatedly, either singly or in combination, throughout this report, it seemed desirable to describe at the outset each group with regard to its purpose, dosage schedule, composition and handling. This is done in detail in table 1.

Group C (C1, C2 and C3).—The C groups served two purposes: (1) to determine the plasma quinacrine absorption curves during the twenty-four to forty-eight hours after the ingestion of single doses of quinacrine at different plasma concentrations of the drug and (2) to determine the effect of larger initial ("priming") doses on the time required to reach a predetermined level of plasma quinacrine. These groups received higher initial doses (0.2 Gm. to 0.3 Gm. per day) followed after varying periods by a maintenance dosage regimen (0.1 Gm. per day). The individual subgroups were small: 4, 4 and 6 men respectively. These men had finished basic and battle training. They performed company duty and lived in regular army barracks.

ARTC Groups (Company B, Sections 1 and 2, Company C, Sections 1 and 2).—These groups, obtained from the Armored Replacement Training Center, served to determine the equilibrium levels of plasma quinacrine attained by large groups of men placed on two constant suppressive dosage regimens of 0.4 Gm. and 0.6 Gm. of quinacrine per week (tables 1 and 2). Because of the dosage and bleeding schedules and the large number of blood samples requiring analysis it was necessary during the first nine weeks of the eleven weeks of suppressive

4. Analytic difficulties with the specimens taken on the following dates gave basis for questioning the reliability of the values obtained: jungle groups, Sept. 11, 1943 (H_{2+5} only), Sept. 13, 1943, Sept. 20, 1943 and Oct. 27, 1943; Company B, Section 1, Oct. 15, 1943, and Oct. 18, 1943; Company B, Section 2, Oct. 27, 1943, and Company C, Section 2, Sept. 18, 1943.

therapy to modify the two dosage regimens from the standard schedules of the Surgeon General's Office.[5] During the last two weeks the regimens were in strict accordance with the schedules of the Surgeon General's Office. During the ensuing twelfth week the drug was withheld from half of the men in order that the curve of disappearance of plasma quinacrine ("die-away") with discontinuance of the drug might be determined. The other half of the men were placed on a modified



* Detailed breakdown of daily dosage and relation of bleeding to dosage is given in table 2.
† Therapeutic dosage, details of which are given in table 2.

therapeutic dosage[5] of quinacrine. This permitted the determination of the therapeutic plasma quinacrine levels and their relationship to suppressive levels in the same men. At the onset of the study 200 men, divided in four sections of 50 men each, comprised this group; at the end 168 men remained; 32 men were lost for varying reasons not associated with the experiment. All men in the ARTC group were in basic training and throughout the study lived the life of such soldiers in all respects.

5. The Drug Treatment of Malaria, Suppressive and Clinical, Circular Letter No. 153, Office of the Surgeon General, War Department, J.A.M.A. **123**:205 (Sept. 25) 1943.

Jungle Groups A and B.—These groups served to determine the effect of humid (jungle) heat, with its profuse sweating, on the level of plasma quinacrine attained on a standard suppressive regimen and, incidentally, the effect of quinacrine on the ability of men to acclimatize and work in humid heat. Since the dosage during the first week was twice the maintenance dosage, the effect of a short "priming" schedule on the time to reach maintenance levels was also obtained. Moreover, the discontinuance of the drug after eleven weeks of suppressive therapy with its resumption after one and two weeks permitted the study of the effect of interruption of dosage.

TABLE 2.—*Dosage and Sampling Schedules for Companies B and C, Fifth Battalion, ARTC (Doses in Grams)*

	Weeks One Through Nine						
	Sun.	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.
Co. B Section 1	No drug	H_2 & H_{2-5} 0.10	0.10	0.05	0.05	H_1 0.05	0.05
Co. B Section 2	No drug	0.10	0.10	H_2 & H_{2-5} 0.10	No drug	H_1 0.10	0.20
Co. C Section 1	No drug	0.05	H_2 & H_{2-5} 0.10	0.10	0.05	0.05	H_1 0.05
Co. C Section 2	No drug	0.10	0.10	0.10	H_2 & H_{2-5} 0.10	No drug	H_1 0.20
	Weeks Ten and Eleven						
Co. B Section 1	0.05	H_2 0.10	H_1 0.05	0.05	0.05	0.05	0.05
Co. B Section 2	0.10	0.10	0.10	H_2 0.10	No drug	H_1 0.10	0.10
Co. C Section 1	0.05	0.05	H_2 0.10	H_1 0.05	0.05	0.05	0.05
Co. C Section 2	0.10	0.10	0.10	0.10	H_2 0.10	No drug	H_1 0.10
	Week Twelve						
Co. B both sections	0.50	0.30	0.30	0.30	H_a 0.30	H_b 0.30	H_c 0.10
Co. C both sections	No drug	H_x No drug	No drug	H_y No drug	No drug	No drug	H_z No drug

Blood sampling schedule: H_1 and H_2 = 11:30 a.m.; H_{2-5} = 4:30 p.m.; $H_{a,b,c}$ = samples during therapeutic dosage; $H_{x,y,z}$ = samples during die-away.

Thirty men who had recently finished basic and battle training were divided into two equal and comparable groups A and B. While one group was living and working in the humid (jungle) heat of the hot room the other group was living and working in the summer out-of-doors of the post. Both groups received exactly the same dosage of quinacrine according to the same schedule; 1.2 Gm. per week for the first week and 0.6 Gm. per week for the next ten weeks. After seven weeks the two groups were switched with regard to the environment alone; the hot room group moving out-of-doors and the out-of-doors group going into the hot room.

Control of Dosage.—In order to insure complete control of drug intake, the quinacrine hydrochloride (0.1 Gm. tablets) was always given under the actual supervision of personnel from the laboratory.

Bleeding Schedule.—The detailed sampling plans are given in their corresponding sections. The design for the regularly scheduled dosage patterns was to secure the minimum levels of the week from bloods drawn twenty-four or more hours after the last dose and the maximum level of the week from bloods drawn five hours after the last or largest dose of the week. The sample for the minimum level is designated as H_1, the level before the last or largest dose of the week as H_2 and the maximum level, drawn five hours after the H_2 sample, as H_{2+5}.

Expression of Results.—Plasma concentrations are expressed as micrograms of quinacrine (base) per liter of plasma. The expression of the central tendency chosen to represent group results was the geometric mean, written "$MEAN_G$." The use of the geometric mean rather than the median or the arithmetic mean was based on the distribution of the data, which in all cases showed better fit with a logarithmic probability curve than with an arithmetic probability curve. This is more extensively considered in section IV.

I. PLASMA QUINACRINE CONCENTRATION FOLLOWING SINGLE ORAL DOSES

The course of rise and fall of plasma quinacrine in the hours immediately following a single oral dose of the drug was followed after the first dose and at several periods during a regular schedule of quinacrine intake. It was hoped in this way that a more detailed picture might be gained of quinacrine levels in the larger groups where sampling was possible less frequently.

Procedure.—The subjects of groups C1, C2 and C3 served for this study. Details of their dosage regimens are indicated in table 1. The absorption curves were determined after single oral doses of 0.2 Gm. (groups C1 and C2) and 0.3 Gm. (group C3) at several stages during the course of the dosage schedules indicated in table 1, i. e., at various levels of plasma quinacrine.

Blood samples (30 cc.) for determination of absorption curves were taken before the drug was given and two, four, six, eight, twelve, twenty-four and, at times, forty-eight hours after the dose. In addition, samples were obtained regularly three times weekly in accordance with the bleeding plan described in the introduction.

Results.—The rise and fall of the plasma quinacrine concentration immediately following a single oral dose of 0.2 Gm. is shown in chart 1. The lowest curve represents the response to the first dose of quinacrine. The rapid rise in plasma level in two hours indicates rapid absorption of the drug. The level is maintained until the fourth hour and then gradually declines. At twenty-four hours there is still an appreciable amount of quinacrine present, suggesting that another dose taken at this

time would produce a superposition of its response curve on the starting level. That this is the case is indicated by the second curve from the bottom of chart 1, which charts the plasma levels after the fourth daily dose of 0.2 Gm. Here the starting level of 9 micrograms per liter results from the accumulation of the preceding three doses. This curve again indicates a rapid rise in two hours, but now the peak level appears to persist for nearly eight hours before falling. The twenty-four hour level again indicates that a net daily gain in plasma level is still occurring at this stage of a daily intake of 0.2 Gm. per day. The uppermost curve, which presents the results after the sixteenth daily dose of 0.2 Gm.,

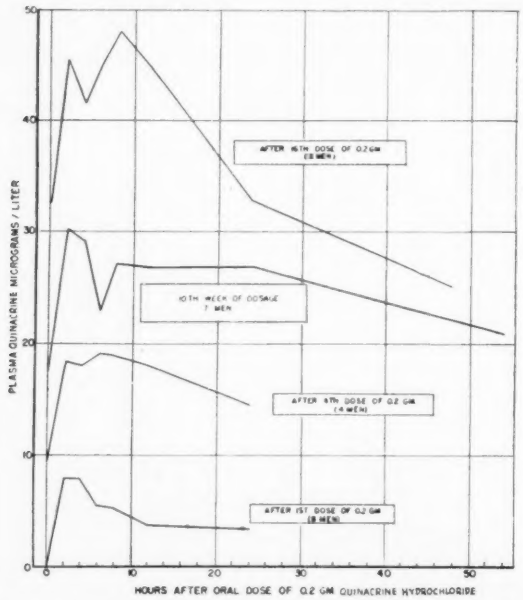


Chart 1.—Postabsorption curves of plasma quinacrine concentration following 0.2 Gm. dose.

shows, first, that a plasma accumulation of better than 30 micrograms per liter has resulted from the previous fifteen doses and, second, that at this high concentration the rate of loss from the plasma has so increased that in twenty-four hours the plasma level has fallen to its predosage level. This suggests that a state of equilibrium has been attained for this rate of intake, that is, that rate of loss from the plasma over twenty-four hours is now equal to the daily intake of the drug. After seventeen daily doses of 0.2 Gm. the dose was reduced to 0.1 Gm. per day, six days a week. The third curve from the bottom of chart 1 demonstrates the response to a dose of 0.2 Gm. in the tenth week of dosage.

That 0.1 Gm. per day was not sufficient to maintain the plasma quinacrine level achieved by the higher rate of intake is indicated by the lower initial level than that found before the sixteenth dose of 0.2 Gm. The plasma quinacrine concentration had dropped from its higher level and was in equilibrium with respect to the dosage rate of 0.1 Gm. per day. Hence the test dose here used results in a net gain in level over a twenty-four hour period.

All the absorption curves except the first show two peaks: an initial one at two hours and a second at six to eight hours. The flattening of the first curve after six hours suggests that even in this curve the phenomena which lead to an eight hour peak may be operative but are less prominent than later. Though scanty, the data suggest that the

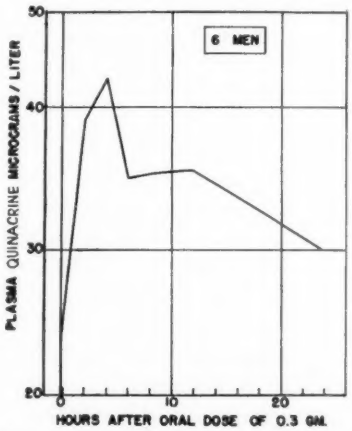


Chart 2.—Postabsorption curve of plasma quinacrine concentration following fourth daily dose of 0.3 Gm.

bimodality of the curves is real and that the second peak shows progressive intensification with continued intake of quinacrine.

The rise in the plasma quinacrine level during the first two hours after ingestion of 0.2 Gm. of the drug appears to increase from about 8 micrograms per liter after the first dose to about 13 micrograms per liter after the sixteenth dose. If this initial rise represents the flooding of the organism with quinacrine during the rapid phases of absorption and distribution, it would be expected that as the tissues become more and more saturated introduction of a given quantity would result in higher peak values.

Chart 2 presents the plasma quinacrine levels after the fourth dose of 0.3 Gm. This curve, except for the anticipated greater rise, is very similar to the curves in chart 1 where the dose was 0.2 Gm. A more

detailed discussion of the form of these curves and their mathematical expression is presented in another report.[6]

In summary, the present data indicate that after a dose of quinacrine the plasma quinacrine level rises rapidly. The major portion of the rise occurs in two hours, and the peak level is reached within eight hours. The form of the absorption curve changes with a continued intake of the drug, the delayed peak being more prominent in the late than in the early course of the dosage regimen. The increase in peak concentration over the starting level increases with continued dosage. After eight hours the plasma quinacrine level starts to fall; the rate of disappearance is more rapid at the higher levels. The net gain in level over a twenty-four hour period decreases with continued intake of the same dose, until finally the rate of disappearance comes abreast of the rate of rise and no increase in level is present at twenty-four hours.

II. PLASMA CONCENTRATIONS RESULTING FROM SEVERAL DOSAGE REGIMENS

Three types of dosage regimens were employed: (1) Uniform rate of intake of quinacrine at a suppressive dosage. Two levels of intake were studied, 0.4 Gm. per week and 0.6 Gm. per week. Approximately 100 men received each level of dosage (ARTC groups). (2) Preparatory administration at a high intake—"booster" or "priming" doses—followed by reduction to a maintenance dosage of 0.6 Gm. per week. Three priming schedules were studied: *(a)* The first consisted of six daily doses of 0.2 Gm. preceding the maintenance dose of 0.1 Gm. per day, six days a week (0.6 Gm. per week). This was carried out on 30 men (jungle groups A and B). *(b)* The second consisted of seventeen doses of 0.2 Gm. per day (8 men) (groups C1 and C2). *(c)* The third consisted of six doses of 0.3 Gm. per day, then six doses of 0.2 Gm. per day and finally the maintenance dose of 0.1 Gm. per day. 0.6 Gm. per week (6 men) (group C3). (3) Therapeutic levels of intake: Approximately 80 men received quinacrine according to a modification of the recommended army therapeutic schedule[5] (ARTC group, Company B, Section 1 and Section 2).

1. *Uniform Dosage.*—Procedure: Companies B and C of the ARTC each supplied 100 men for this portion of the study. Each group of 100 men was subdivided into two sections of 50 men each. One section from each group received 0.4 Gm. of quinacrine hydrochloride per week, and the second section of each group, 0.6 Gm. per week. The dosage and bleeding schedules are given in tables 1 and 2.

Quinacrine was administered by roster at the noon mess by a medical officer assigned to the project. When Company B was placed on full

6. Brackett, F. S.: To be published.

therapeutic doses, the drug was administered at each meal. In the fourth week it was discovered that 1 subject had been able to spit out the tablet in spite of the careful supervision of administration by the officer. Thereafter, at intervals, the oral cavities were examined after administration of the drug. As an added check 6 of the men having the lowest plasma levels were given the drug in solution for a period of two weeks. During this time no change occurred in the plasma levels of these men.

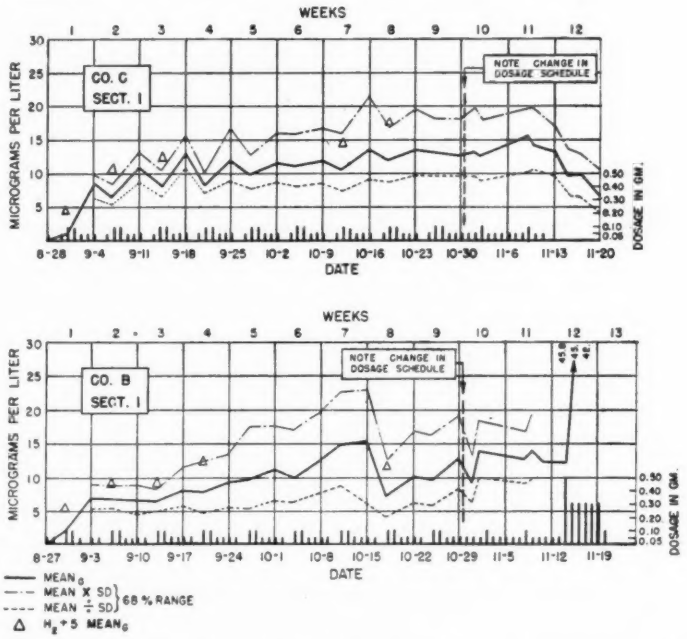


Chart 3.—MEAN$_G$ plasma quinacrine levels of two groups of men receiving 0.4 Gm. per week.

Blood samples for underlying levels were taken at 11 : 30 a.m., prior to the noon mess; the first such sample of the week was designated H_1, the second H_2. The blood samples for peak concentrations were taken at 4 : 30 p.m., five hours after ingestion of the drug. These were designated H_{2+5}.

Results.—The characteristic behavior of the group mean plasma quinacrine levels is indicated by charts 3 and 4, which show that the time required to reach the equilibrium level was in general the same—

without regard to the magnitude of the dose.[7] Individual variability with respect to this trend was wide, as will be seen later. For example, in two weeks approximately 8 per cent reached a level from which they did not subsequently depart significantly. Fourteen per cent appeared to have reached equilibrium levels at the end of the fourth week, whereas 9 per cent may be considered to have not yet become stabilized in seven weeks, since their highest plasma levels occurred during the eighth to eleventh weeks. When, therefore, one speaks of the attainment of equilibrium levels with a given dosage, it is to be

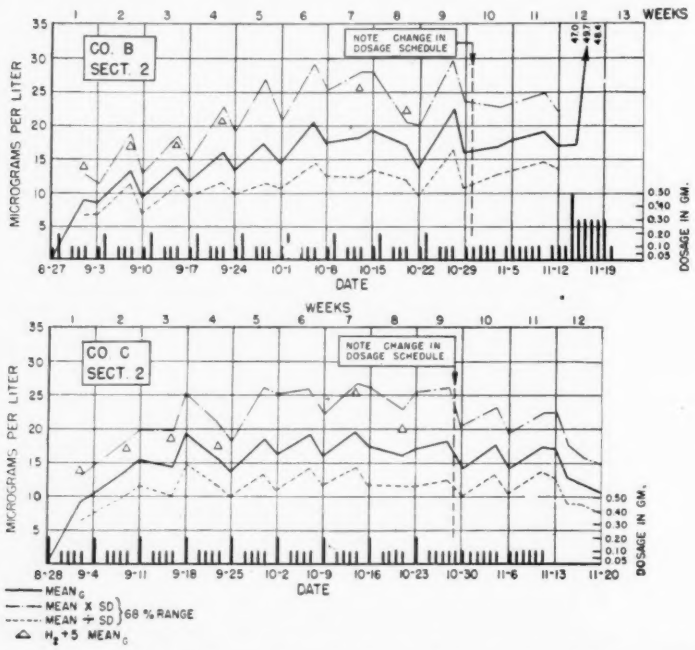


Chart 4.—MEAN$_G$ plasma quinacrine levels of two groups of men receiving 0.6 Gm. per week.

recognized that this is a term of convenience. It remains a concept which is applicable to the mean plasma quinacrine level for a group and not to the level for an individual within the group. During the second and third weeks the rates of increase in plasma quinacrine were

7. The apparently irregular rhythmic behavior of certain groups is the result of a differing interval between dosage and sampling. The erratic results obtained on one day's sample in the week of October 15 (chart 3) and the week of October 22 (chart 4) were the result of aberrations in the chemical method which affected all samples on that day.

quite constant; accordingly, individual subjects who became stabilized in the earlier weeks in general did so at levels which were lower than those of subjects who reached their equilibrium levels in the sixth or seventh weeks.

The group mean plasma levels at equilibrium were found to be directly proportional to the dosages (chart 5); with a regimen of 0.4 Gm. per week the level was 12.2 micrograms per liter, and with 0.6 Gm. per week the mean was 17.2 micrograms per liter. These are the $MEAN_G$ values of all H_1 measurements of weeks 7 to 11 inclusive. Alterations in time relationship between dosage and sampling may change group values. However, when the dosage pattern was changed from that regularly followed to that recommended by the Surgeon General's Office, no differences in mean plasma levels were noted (charts 3, 4

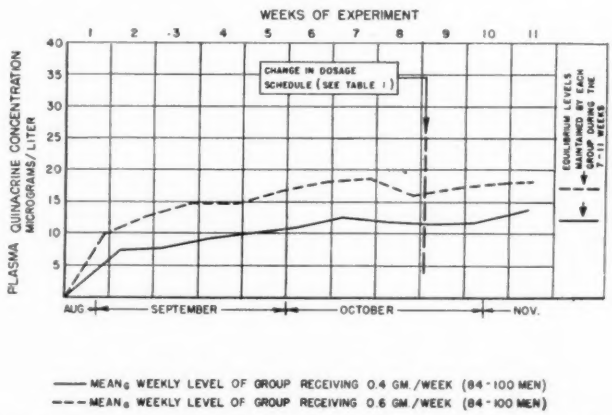

WEEKS OF EXPERIMENT
1 2 3 4 5 6 7 8 9 10 11
PLASMA QUINACRINE CONCENTRATION MICROGRAMS/LITER
40 35 30 25 20 15 10 5
CHANGE IN DOSAGE SCHEDULE (SEE TABLE 1)
EQUILIBRIUM LEVELS MAINTAINED BY EACH GROUP DURING THE 7-11 WEEKS
AUG. SEPTEMBER OCTOBER NOV.
MEAN$_G$ WEEKLY LEVEL OF GROUP RECEIVING 0.4 GM./WEEK (84-100 MEN)
MEAN$_G$ WEEKLY LEVEL OF GROUP RECEIVING 0.6 GM./WEEK (84-100 MEN)

Chart 5.—Comparison of $MEAN_G$ weekly plasma quinacrine levels of two groups of men on different dosage schedules (H_1 values).

and 6). The group data are tabulated in tables 3, 4, 5 and 6 by sections and are grouped according to dose in table 7.

2. *Effect of Initial Priming Dose.* Procedure: The experimental data illustrating the influence of priming doses are drawn from the jungle groups A and B, groups C1, C2 and C3 and the ARTC groups from Company B and Company C. After the initial priming or equivalent period the dosage of each of these groups was stabilized at a maintenance dose of 0.6 Gm. per week. The priming schedules were (in order) six daily doses of 0.2 Gm. (jungle groups A and B), seventeen daily doses of 0.2 Gm. (groups C1 and C2), six daily doses of 0.3 Gm. followed by six daily doses of 0.2 Gm. (group C3) and no priming dose (ARTC Companies B and C) (table 1).

TABLE 3.—*Mean$_G$ and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Company B, Section 1 (Receiving 0.4 Gm. per Week)*

Week No.	Week Date	Number of Men	Mean$_G$	68% Range of Mean$_G$	Dispersion σ_G	Dispersion 68% Range	Mean$_A$
			Bleeding H_1				
2	Sept. 3	49	6.7	6.4 - 6.9	1.32	5.1 - 8.6	6.7
3	10	48	6.3	4.8 - 6.6	1.39	4.5 - 8.8	6.4
4	17	45	8.0	7.6 - 8.4	1.39	5.8 - 11.2	8.4
5	24	43	9.1	8.4 - 9.9	1.72	5.3 - 13.2	11.4
6	Oct. 1	41	11.0	9.9 - 11.6	1.65	6.5 - 17.7	12.8
7	8	41	12.5	11.6 - 13.4	1.58	7.9 - 19.7	15.0
8	15	40	15.2	14.6 - 16.2	1.50	10.1 - 22.7	16.7
9	22	41	10.0	9.4 - 11.0	1.64	6.2 - 16.7	11.5
10	29	36	12.7	11.9 - 13.6	1.50	8.5 - 19.0	13.8
10	Nov. 2	42	13.6	12.9 - 14.2	1.36	10.0 - 18.4	14.3
11	9	41	13.8	13.1 - 14.6	1.40	9.9 - 19.4	14.7
			Bleeding H_2				
1	Aug. 30	50	1.6	.....	....	.....	1.6
2	Sept. 6	46	6.7	6.5 - 7.0	1.28	5.3 - 8.6	6.8
3	13	47	6.3	6.1 - 6.6	1.31	5.0 - 8.3	6.5
4	20	47	7.8	7.3 - 8.3	1.59	4.9 - 12.4	9.2
5	27	44	9.5	8.7 - 10.4	1.78	5.3 - 17.1	11.9
6	Oct. 4	42	10.0	9.6 - 11.1	1.65	6.3 - 17.0	11.8
7	11	41	14.7	13.8 - 15.7	1.53	8.8 - 22.5	16.3
8	18	40	7.2	6.6 - 7.9	1.73	4.2 - 12.5	9.2
9	25	42	9.6	8.9 - 13.1	1.68	5.7 - 16.2	11.2
10	Nov. 1	41	9.1	8.6 - 9.6	1.45	6.3 - 13.1	9.8
11	8	42	12.4	11.9 - 13.0	1.34	9.2 - 16.7	13.0
			Bleeding H_{2+5}				
1	Aug. 30	50	5.2	5.0 - 5.4	1.32	4.0 - 6.8	5.5
2	Sept. 6	49	7.6	7.4 - 7.9	1.29	5.9 - 9.8	7.7
3	13	44	9.0	8.5 - 9.7	1.57	5.8 - 14.2	9.1
4	20	44	12.4	11.7 - 13.1	1.49	8.3 - 18.4	13.6
8	Oct. 18	38	11.8	10.9 - 12.8	1.63	7.3 - 19.3	13.5

TABLE 4.—*Mean$_G$ and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Company C, Section 1 (Receiving 0.4 Gm. per Week)*

Week No.	Week Date	Number of Men	Mean$_G$	68% Range of Mean$_G$	Dispersion σ_G	Dispersion 68% Range	Mean$_A$
			Bleeding H_1				
2	Sept. 4	45	8.5	8.4 - 8.7	1.16	7.4 - 9.9	8.6
3	11	48	10.7	10.4 - 10.9	1.24	8.6 - 13.3	10.9
4	18	44	13.1	12.8 - 13.2	1.20	10.9 - 16.5	13.3
5	25	41	12.1	11.7 - 12.7	1.36	8.9 - 16.5	12.7
6	Oct. 2	43	11.6	11.0 - 12.1	1.36	8.6 - 15.8	12.3
7	9	40	12.0	11.4 - 12.7	1.41	8.5 - 16.9	12.9
8	16	43	13.9	13.0 - 14.9	1.56	9.0 - 21.6	15.4
9	23	42	13.5	12.8 - 14.2	1.41	9.6 - 19.0	14.4
10	30	39	12.7	12.0 - 13.4	1.41	9.0 - 17.8	13.6
10	Nov. 3	42	12.7	12.1 - 13.4	1.42	8.9 - 18.0	13.6
11	10	42	14.3	13.6 - 15.0	1.36	10.5 - 19.4	15.0
			Bleeding H_2				
1	Aug. 31	42	....	.....	....	.....	1.0
2	Sept. 7	45	6.7	6.5 - 6.8	1.26	5.3 - 8.4	6.9
3	14	47	8.3	8.0 - 8.6	1.27	6.5 - 10.5	8.5
4	21	41	8.5	8.3 - 8.7	1.19	7.2 - 10.1	8.7
5	28	43	9.8	9.4 - 10.1	1.29	7.6 - 12.6	10.5
6	Oct. 5	42	11.2	10.7 - 11.8	1.41	8.0 - 15.8	12.1
7	12	40	10.6	10.0 - 11.4	1.50	7.1 - 16.0	11.8
8	19	42	12.0	11.4 - 12.7	1.40	8.6 - 16.8	14.3
9	26	39	13.1	12.5 - 13.8	1.38	9.5 - 18.1	13.8
10	Nov. 2	42	13.2	12.8 - 14.1	1.46	9.0 - 19.3	14.2
11	9	40	13.8	13.1 - 14.5	1.38	10.0 - 19.0	14.6
			Bleeding H_{2+5}				
1	Aug. 31	47	4.6	4.4 - 4.8	1.39	3.3 - 6.4	4.9
2	Sept. 7	46	10.7	10.4 - 11.1	1.23	8.7 - 13.2	10.9
3	14	46	12.3	11.9 - 12.7	1.24	9.9 - 15.2	12.6
4	21	41	11.1	10.7 - 11.5	1.24	8.9 - 13.8	11.4
7	Oct. 12	37	14.4	13.5 - 15.2	1.48	9.7 - 21.3	16.5
8	19	41	17.9	17.1 - 18.8	1.34	13.4 - 24.0	18.7

TABLE 5.—*Mean$_G$ and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Company B, Section 2 (Receiving 0.6 Gm. per Week)*

Week No.	Week Date	Number of Men	Mean$_G$	68% Range of Mean$_G$	Dispersion σ_G	Dispersion 68% Range	Mean$_A$
			Bleeding H_1				
2	Sept. 3	47	8.9	8.6 - 9.3	1.28	6.9 - 11.4	8.8
3	10	45	9.6	9.2 - 10.0	1.43	7.1 - 12.9	9.8
4	17	42	11.8	11.4 - 12.2	1.25	9.5 - 14.7	11.6
5	24	41	13.6	12.9 - 14.3	1.37	9.9 - 18.6	15.1
6	Oct. 1	45	14.7	14.0 - 15.5	1.39	10.6 - 20.5	15.9
7	8	41	17.5	16.5 - 18.4	1.41	12.3 - 24.7	18.4
8	15	40	19.3	18.2 - 20.6	1.46	13.2 - 28.3	18.8
9	22	40	13.6	12.8 - 14.4	1.46	9.3 - 19.8	14.7
10	29	42	16.0	15.0 - 17.0	1.48	10.8 - 23.7	17.0
11	Nov. 5	41	17.9	17.2 - 18.7	1.31	13.7 - 23.6	19.9
12	12	40	17.5	16.9 - 18.2	1.28	13.7 - 22.3	18.1
			Bleeding H_2				
1	Sept. 1	49	9.2	8.8 - 9.7	1.37	6.7 - 12.7	10.0
2	8	45	13.9	13.3 - 14.3	1.25	11.1 - 17.2	13.4
3	15	43	14.2	13.6 - 14.8	1.30	10.9 - 18.4	14.0
4	22	43	16.2	15.4 - 17.1	1.41	11.5 - 22.8	16.0
5	29	44	17.5	16.4 - 18.8	1.56	11.2 - 26.8	18.8
6	Oct. 6	43	20.4	19.3 - 23.1	1.42	14.3 - 29.0	21.8
7	13	44	18.3	17.2 - 19.5	1.58	12.1 - 27.7	21.5
8	20	42	17.3	16.3 - 18.4	1.48	11.7 - 20.3	16.7
9	27	43	22.4	21.4 - 23.3	1.32	16.1 - 29.5	23.5
10	Nov. 3	41	16.9	16.2 - 16.7	1.35	12.6 - 22.8	17.7
11	10	41	19.0	18.1 - 19.7	1.30	14.5 - 24.6	19.6
			Bleeding H_{2-5}				
1	Sept. 1	48	14.1	13.6 - 14.7	1.33	8.5 - 18.8	14.0
2	8	45	16.9	16.3 - 17.6	1.32	12.8 - 22.5	17.0
3	15	44	17.3	16.6 - 18.0	1.29	13.3 - 22.4	18.1
4	22	43	20.8	20.1 - 21.8	1.33	15.7 - 27.7	20.5
7	Oct. 13	44	25.9	24.6 - 27.2	1.39	18.7 - 35.7	28.1
8	20	41	22.1	21.0 - 23.2	1.37	16.1 - 30.3	21.4

TABLE 6.—*Mean$_G$ and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Company C, Section 2 (Receiving 0.6 Gm. per Week)*

Week No.	Week Date	Number of Men	Mean$_G$	68% Range of Mean$_G$	Dispersion σ_G	Dispersion 68% Range	Mean$_A$
			Bleeding H_1				
2	Sept. 4	52	11.2	10.9 - 11.5	1.35	9.0 - 13.9	12.0
3	11	51	15.1	14.5 - 15.6	1.35	11.5 - 19.7	15.6
4	18	48	19.1	18.4 - 20.0	1.31	14.6 - 25.0	19.8
5	25	45	13.6	13.0 - 14.2	1.35	10.0 - 18.3	14.3
6	Oct. 2	46	16.3	15.3 - 16.8	1.54	10.6 - 25.1	17.6
7	9	46	16.8	15.3 - 16.8	1.37	11.7 - 21.9	16.8
8	16	42	17.5	16.4 - 18.6	1.49	11.7 - 26.1	18.8
9	23	44	17.0	16.0 - 18.0	1.49	11.4 - 25.3	18.5
10	30	44	14.4	13.6 - 15.2	1.43	10.1 - 20.5	15.3
11	Nov. 6	44	14.3	13.6 - 14.9	1.35	10.6 - 19.2	15.0
12	13	44	17.0	16.3 - 17.8	1.35	12.8 - 22.5	17.6
			Bleeding H_2				
1	Sept. 2	53	9.1	8.7 - 9.6	1.44	6.4 - 13.1	9.6
2	9	50	13.7	13.1 - 14.3	1.34	10.2 - 18.4	14.2
3	16	45	14.4	13.8 - 15.1	1.38	10.0 - 19.8	15.2
4	23	47	15.4	14.7 - 16.1	1.34	11.5 - 20.6	16.2
5	30	46	18.6	18.5 - 19.7	1.40	13.3 - 26.0	19.9
6	Oct. 7	46	19.3	18.7 - 20.5	1.34	14.4 - 25.9	20.2
7	14	47	19.6	18.7 - 20.5	1.36	14.4 - 26.7	23.0
8	21	44	16.0	15.2 - 16.9	1.42	11.3 - 22.7	17.0
9	28	45	17.8	16.9 - 18.9	1.46	12.3 - 26.0	19.1
10	Nov. 4	44	17.6	16.9 - 18.4	1.32	13.4 - 23.3	18.5
11	11	45	17.4	16.8 - 18.1	1.28	13.7 - 22.2	17.9
			Bleeding H_{2-5}				
1	Sept. 2	52	13.8	13.2 - 14.4	1.37	10.0 - 18.9	12.0
2	9	51	17.2	16.5 - 18.0	1.35	12.8 - 23.3	16.1
3	16	46	18.6	17.8 - 19.5	1.36	13.7 - 25.3	19.6
4	23	47	17.5	16.6 - 18.3	1.42	12.3 - 24.9	18.6
7	Oct. 14	45	25.5	24.4 - 26.7	1.36	18.8 - 34.8	26.8
8	21	44	20.0	19.0 - 21.0	1.36	14.4 - 27.7	21.1

Results.—The plasma quinacrine concentrations resulting from intakes according to these schedules are shown in chart 6. In all cases in which a priming regimen (curves 2, 3 and 4) was used a higher plasma concentration was present at the end of the first week than when no

TABLE 7.—*Mean$_G$ and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter); Tabulated Data for Combined ARTC Groups—Sections 1 and 2 of Companies B and C*

Week No.	Week Date	Number of Men	Mean$_G$	68% Range of Mean$_G$	Dispersion σ_G	Dispersion 68% Range	Mean$_A$
		Groups Receiving 0.40 Gm. per Week					
		Bleeding H_1					
2	Sept. 3 & 4	94	7.5	7.3 - 7.7	1.29	5.8 - 9.7	7.8
3	10 & 11	96	8.2	7.9 - 8.5	1.47	5.6 - 12.0	8.8
4	17 & 18	89	10.2	9.9 - 10.6	1.43	7.1 - 14.7	10.9
5	24 & 25	84	10.4	9.9 - 11.0	1.59	6.6 - 16.7	12.1
6	Oct. 1 & 2	84	11.0	10.6 - 11.5	1.52	7.3 - 16.7	12.5
7	8 & 9	81	12.5	11.7 - 13.1	1.50	8.3 - 18.8	13.9
8	15 & 16	83	14.5	13.8 - 15.2	1.53	9.5 - 22.2	15.5
9	22 & 23	83	11.7	11.2 - 12.3	1.56	7.5 - 18.4	13.0
10	29 & 30	75	12.7	12.2 - 13.2	1.45	8.7 - 18.4	13.7
10	Nov. 2 & 3	84	13.1	12.6 - 13.6	1.40	9.4 - 18.3	13.9
11	9 & 10	83	14.0	13.5 - 14.5	1.38	10.2 - 19.3	14.7
		Bleeding H_2					
2	Sept. 6 & 7	91	6.7	6.6 - 6.9	1.27	5.3 - 8.5	6.9
3	13 & 14	94	7.2	7.1 - 7.4	1.29	5.6 - 9.3	7.5
4	20 & 21	88	8.1	7.8 - 8.4	1.43	5.7 - 11.7	9.0
5	27 & 28	87	9.6	9.2 - 10.1	1.58	6.1 - 15.2	11.2
6	Oct. 4 & 5	84	10.8	10.2 - 11.3	1.54	7.0 - 16.5	11.9
7	11 & 12	81	12.5	11.8 - 13.3	1.56	8.0 - 19.6	14.1
8	18 & 19	82	9.4	9.0 - 9.8	1.53	6.1 - 14.4	11.8
9	25 & 26	81	11.2	10.6 - 11.8	1.58	7.1 - 17.7	12.4
10	Nov. 1 & 2	83	11.0	10.5 - 11.5	1.52	7.2 - 16.7	11.7
11	8 & 9	82	13.0	12.6 - 13.5	1.37	9.5 - 17.8	13.8
		Groups Receiving 0.60 Gm. per Week					
		Bleeding H_1					
2	Sept. 3 & 4	99	10.0	9.7 - 10.4	1.30	7.7 - 13.1	10.6
3	10 & 11	96	12.2	11.8 - 12.6	1.34	9.1 - 16.3	12.8
4	17 & 18	90	15.3	14.9 - 15.7	1.30	11.8 - 19.8	15.9
5	24 & 25	86	13.6	13.2 - 14.0	1.33	10.2 - 18.0	14.7
6	Oct. 1 & 2	91	15.5	14.9 - 16.1	1.48	10.5 - 22.8	16.7
7	8 & 9	87	16.7	16.1 - 17.3	1.43	11.7 - 23.9	17.7
8	15 & 16	82	18.4	17.6 - 19.2	1.48	12.4 - 27.3	20.0
9	22 & 23	84	15.3	14.6 - 16.0	1.50	10.2 - 22.9	16.6
10	29 & 30	86	15.1	14.5 - 15.8	1.46	10.3 - 22.1	15.6
11	Nov. 5 & 6	84	16.5	15.9 - 17.0	1.35	12.2 - 22.2	17.5
		Bleeding H_2					
1	Sept. 1 & 2	102	9.1	8.8 - 9.4	1.41	6.5 - 12.8	9.8
2	8 & 9	95	13.7	13.2 - 14.3	1.30	10.6 - 17.8	14.1
3	15 & 16	88	14.3	13.9 - 14.8	1.34	10.7 - 19.2	14.9
4	22 & 23	90	15.8	15.3 - 16.3	1.37	11.5 - 21.6	16.7
5	29 & 30	90	18.1	17.3 - 18.8	1.49	12.5 - 26.8	19.3
6	Oct. 6 & 7	89	19.8	19.1 - 20.5	1.39	14.3 - 27.4	21.0
7	13 & 14	91	18.9	18.2 - 19.7	1.44	13.1 - 27.3	22.2
8	20 & 21	86	16.6	16.0 - 17.3	1.45	11.4 - 24.1	17.9
9	27 & 28	88	19.9	19.2 - 20.7	1.42	14.0 - 28.3	19.3
10	Nov. 3 & 4	85	17.3	16.8 - 17.8	1.33	13.0 - 23.0	18.1
11	10 & 11	86	18.1	17.6 - 18.6	1.29	14.0 - 23.4	18.7

priming dose was given (curve 1). Compare the curve (curve 1) of the mean plasma level for the ARTC group on a constant schedule of 0.6 Gm. per week with the curve (curve 2) for the jungle group, which received an initial booster dose of 1.2 Gm. per week for the first week. In the groups C1 and C2 (curve 3) and group C3 (curve 4) plasma concentrations in excess of the ultimate maintenance level were reached

within a week. However, the time required to reach the final equilibrium plasma quinacrine level was not changed. Instead it was approached by a declining concentration curve from higher levels in contrast to the progressively rising curves for the group receiving no booster dose. The jungle group (curve 2), receiving twice the maintenance dose for the first week, reached a plasma concentration close to its final equilibrium level at the end of the first week, declined slightly during the second week and thereafter was in close agreement with the level of the ARTC group (curve 1) receiving maintenance dosage from the outset. The equilibrium levels finally attained on the maintenance regimen of

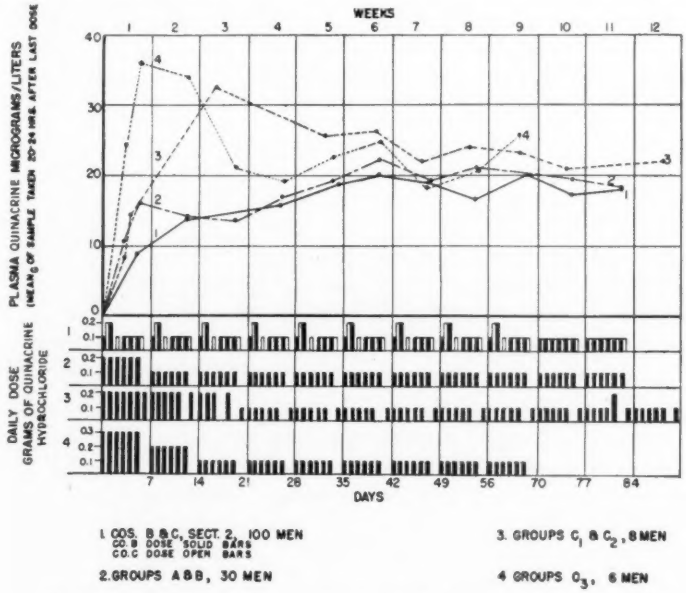

WEEKS
1 2 3 4 5 6 7 8 9 10 11 12
PLASMA QUINACRINE MICROGRAMS/LITERS (MEAN OF SAMPLE TAKEN 20-24 HRS. AFTER LAST DOSE)
40
30
20
10
0
DAILY DOSE GRAMS OF QUINACRINE HYDROCHLORIDE
0.2
0.1
0.3
7 14 21 28 35 42 49 56 70 77 84
DAYS
1. COS. B & C, SECT. 2, 100 MEN
CO. B DOSE SOLID BARS
CO. C DOSE OPEN BARS
2. GROUPS A & B, 30 MEN
3. GROUPS C_1 & C_2, 8 MEN
4. GROUPS C_3, 6 MEN

Chart 6.—Plasma quinacrine levels obtained with different priming doses (maintenance dosage, 0.6 Gm. per week).

0.6 Gm. per week did not differ significantly among the four groups. Since the rapidity with which an effective suppressive plasma quinacrine level is reached may be an important factor in operations in malarious areas, the practical significance of initial high dosage schedules is great.

Of considerable practical advantage in the design of such schedules is the technic of prediction of plasma concentration as a function of dosage as given in section IV. For example, the rate of rise in plasma level in any week is approximately 50 per cent of the difference between the level already established and the final equilibrium level. Then

for dosages of 0.6 Gm. per week and 1.2 Gm. per week the predicted plasma levels at the end of succeeding weeks will be:

Week	Plasma Concentration	
	0.6 Gm./Wk.	1.2 Gm./Wk.
1	9.0	18.0
2	13.5	27.0
3	15.7	31.5
4	16.9	33.7
5	17.4	34.8
Equilibrium	18.0	36.0

At the higher dosage rate of 1.2 Gm. per week the plasma level at the end of the first week is as high as the equilibrium level ultimately attained by a dosage of 0.6 Gm. per week. Thus, if the dosage during the first week is twice the subsequent maintenance dosage, the plasma concentration will be raised to the desired level in one week rather than in the five to seven weeks which are required when no "booster" dose is given.

3. *Plasma Levels Obtained with Therapeutic Doses.*—Procedure: After having reached equilibrium levels on their respective dosage schedules of 0.4 Gm. per week and 0.6 Gm. per week, the two sections of Company B, ARTC group, were placed on a modified therapeutic regimen at the beginning of the twelfth week. The dosage schedule was as follows: the first day, 0.5 Gm. (0.1 Gm. at breakfast and 0.2 Gm. at lunch and supper); the next five days, 0.3 Gm. (0.1 Gm. at breakfast, lunch and supper), and the seventh day, 0.1 Gm. at breakfast. Blood samples were taken before the noon meal on the fourth, fifth and sixth days.

Results.—The increases in plasma levels for the two sections at the end of six days were approximately the same, 30.8 and 30.5 micrograms per liter respectively above their previously established equilibrium levels (chart 7). The changes in plasma concentration induced by the therapeutic dosage regimen followed the same basic law of build-up as that previously determined for suppressive regimens with lower doses. An important objective was to determine whether men with persisting low or high plasma levels while on suppressive therapy would continue in the same relation to the group mean when receiving therapeutic doses of quinacrine. The correlations are shown in charts 8 and 9. Chart 8 shows the distribution of the equilibrium levels attained under the two suppressive regimens and the subsequent distribution of the low, central and high levels following the institution of therapeutic doses. No great shift in distribution occurred; the plasma levels tended to retain their original relationship to each other. The correlation is shown in another way in chart 9, where the level attained by therapeutic doses is plotted against the level attained on suppressive doses. A definite relationship is evident, but the correlation is not high. One

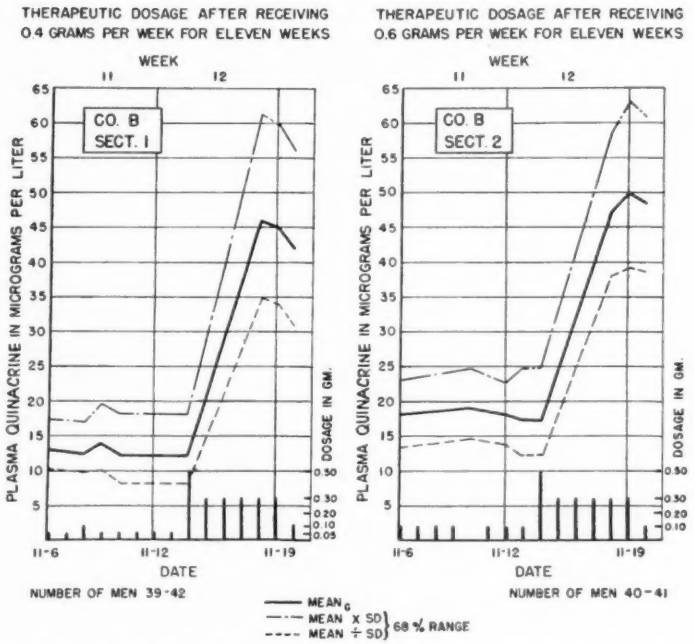


Chart 7.—MEAN$_G$ plasma quinacrine levels of two groups of men receiving therapeutic dosage for one week.

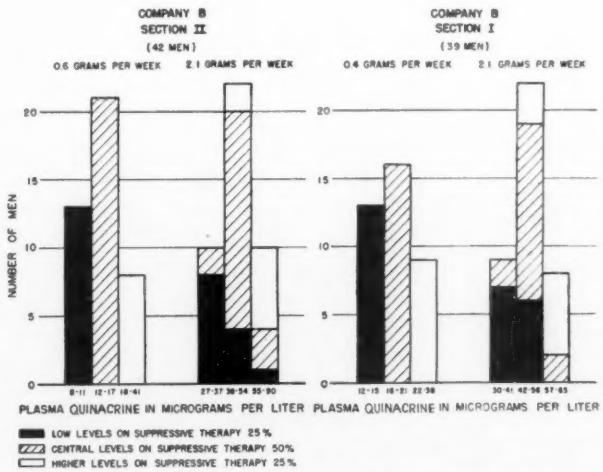

COMPANY B SECTION II (42 MEN)
0.6 GRAMS PER WEEK
2.1 GRAMS PER WEEK
COMPANY B SECTION I (39 MEN)
0.4 GRAMS PER WEEK
2.1 GRAMS PER WEEK
NUMBER OF MEN
PLASMA QUINACRINE IN MICROGRAMS PER LITER
PLASMA QUINACRINE IN MICROGRAMS PER LITER
LOW LEVELS ON SUPPRESSIVE THERAPY 25 %
CENTRAL LEVELS ON SUPPRESSIVE THERAPY 50%
HIGHER LEVELS ON SUPPRESSIVE THERAPY 25 %

Chart 8.—Relationship between the level attained on suppressive therapy and the level reached on therapeutic doses.

cannot predict with certainty the relative level for a subject receiving therapeutic doses from his relative level while on suppressive doses, except in broad categories. The group data are assembled in table 8.

TABLE 8.—*Plasma Quinacrine Levels (Micrograms per Liter) of Group of Men (Company B) Receiving Therapeutic Dosage After Eleven Weeks of Suppressive Dosage*

Week		Number of Men			Dispersion		
No.	Date		$Mean_G$	68% Range of $Mean_G$	σ_G	68% Range	$Mean_A$
			Company B Section 1				
12	Nov. 18	42	45.9	44.0 - 48.0	1.33	34.6 - 61.0	47.9
13	19	41	45.0	43.1 - 47.1	1.33	33.8 - 59.8	47.0
13	20	39	42.0	40.1 - 44.0	1.33	30.8 - 56.0	46.6
			Company B Section 2				
12	Nov. 18	40	47.0	43.1 - 48.6	1.25	37.7 - 58.5	48.1
13	19	41	49.7	47.8 - 51.5	1.27	39.0 - 63.2	51.1
13	20	41	48.4	46.7 - 50.1	1.26	38.6 - 60.8	49.6

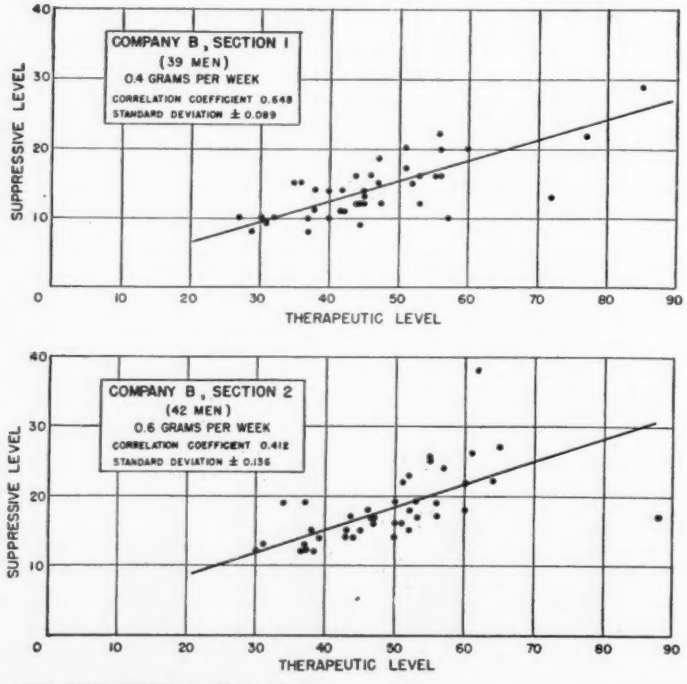


Chart 9.—Relationship between the plasma quinacrine level attained on suppressive therapy and the level reached on therapeutic doses.

III. PLASMA CONCENTRATIONS AFTER CESSATION OF DOSAGE AND AFTER INTERRUPTION OF DOSAGE

Procedure.—At the end of the eleventh week jungle group B was removed from the humid heat, and administration of quinacrine to both groups was discontinued in order to study the rate of fall of the plasma quinacrine level (die-away). The subsequent increase in concentration on restoration of suppressive doses of quinacrine (build-up) at different points on the plasma die-away curve was also determined. Half of the men were without the drug for one week and the other half for two weeks. To insure comparability of the two die-away curves, groups A and B were rearranged into two new groups (X and Y) which were comparable with respect to: duration of previous exposure to heat, time since removal from the humid heat, weight of the men, plasma quinacrine level over the four week period before cessation of dosage and quinacrine levels after six days without the drug. Quinacrine in suppressive doses (0.1 Gm. per day) was resumed in group X after an interval of one week and in group Y after two weeks.

To obtain additional information on larger numbers of men concerning the die-away curve of plasma quinacrine after cessation of dosage the drug was discontinued in ARTC groups Company C, Section 1 (0.4 Gm. per week) and Company C, Section 2 (0.6 Gm. per week) for one week after eleven weeks of suppressive therapy. Blood samples were obtained at the beginning, middle and end of the week.

Results.—Die-away: After the intake of quinacrine has been discontinued, the plasma concentration of quinacrine falls off according to a normal decay curve, rapidly at first, then progressively more slowly as the level approaches zero. The pattern of disappearance indicates a rate of elimination and degradation which is proportional to the level. The slow rate of disappearance is consonant with the observed slow attainment of equilibrium levels and probably results from two characteristic features of quinacrine metabolism, the extensive tissue storage and the very low concentration in plasma. These two factors, the large amount to be disposed of and low carrying capacity in the path of elimination, combine to produce a slow rate of disappearance of the drug. Chart 10 shows the fall in plasma level in groups X and Y. Chart 11 shows the plasma decay curves for the larger ARTC groups. The latter data plotted on semilogarithmic scale in chart 12 illustrate the exponential nature of the disappearance of quinacrine from the plasma. The slopes of the lines indicate a 10 per cent reduction in plasma level per day, a 50 per cent reduction per week and a 75 per cent reduction in two weeks. This is very similar to the rate of approach to equilibrium levels for a uniform rate of intake. The theoretic basis for this is considered in another report [6] and in section IV. The means

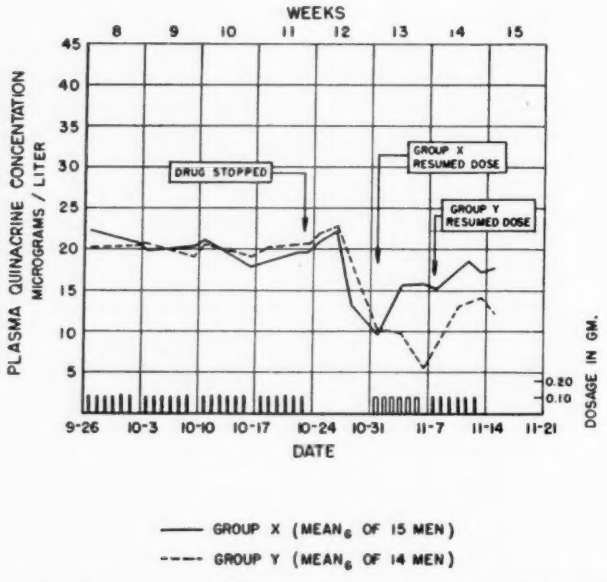


Chart 10.—Influence of the interruption of dosage on the plasma quinacrine levels (30 men receiving weekly dosage of 0.6 Gm.).

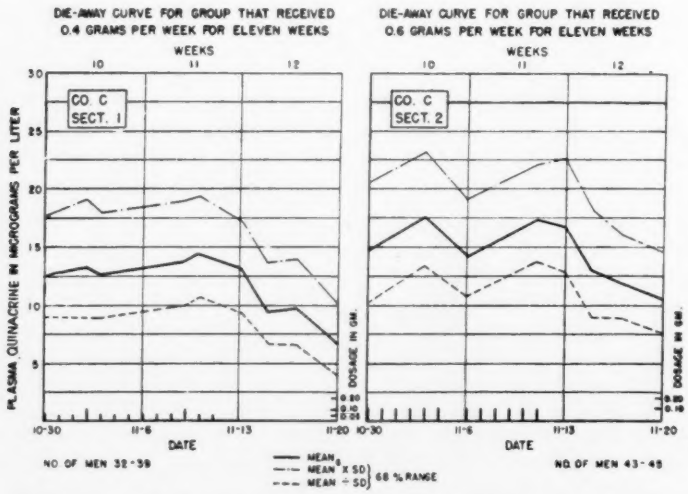


Chart 11.—MEAN$_6$ plasma quinacrine levels of two groups of men for one week after discontinuance of suppressive therapy.

and dispersions for the X and Y groups are recorded in table 9 and the die-away data for the ARTC groups in table 10.

Interruption of Dosage.—After quinacrine had been discontinued in group X for one week and in group Y for two weeks, dosage was resumed according to the previous schedule of 0.6 Gm. per week. The results are shown in chart 10. In each instance the rate of increase in the plasma levels of quinacrine was consonant with the findings in other groups at the start of dosage taking into account the higher start-

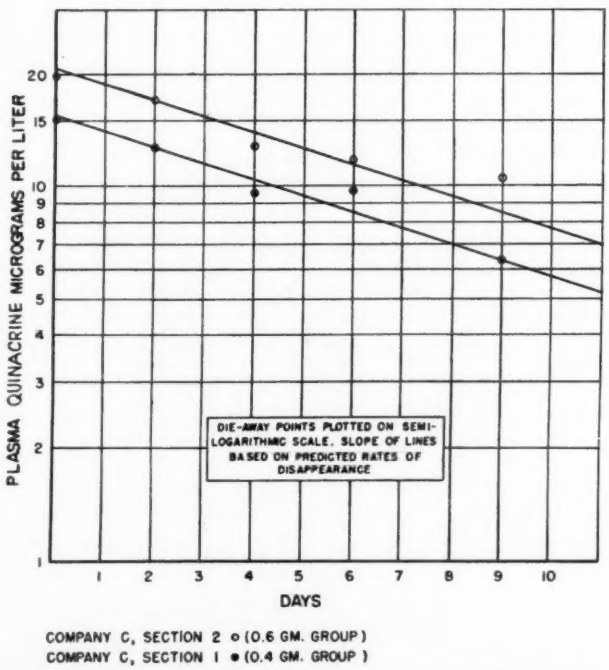


Chart 12.—Exponential nature of the disappearance of quinacrine from the plasma when dosage is discontinued.

ing levels; this is also illustrated by the close correspondence of the observed rate of build-up with predicted rates of build-up as shown in chart 20. It appears, therefore, that reestablishment of suppressive levels after interruption of dosage presents no unique features; if dosage is resumed while quinacrine is still present in the plasma, the return to equilibrium levels will be hastened in proportion to the plasma quinacrine level when dosage is resumed.

TABLE 9.—*Mean Plasma Quinacrine Levels of Men in the Jungle Group Rearranged for Study of Die-Away and Recovery (H_1 and H_2 Bleedings Only)*

Week No.	Week Date	Number of Men	$Mean_G$	68% Range of $Mean_G$	Dispersion σ_G	Dispersion 68% Range	Dispersion $Mean_A$
			All Bleedings Group X				
8	Sept. 27	14	22.2	19.9 - 24.8	1.51	14.8 - 33.5	24.1
8	Oct. 2	15	20.7	19.0 - 22.6	1.40	14.7 - 29.0	22.0
9	4	15	19.9	18.0 - 21.9	1.46	13.7 - 29.0	21.5
9	9	14	20.3	17.3 - 22.1	1.45	16.6 - 34.8	21.8
10	11	15	21.1	19.4 - 23.0	1.39	15.2 - 29.4	22.3
10	16	14	17.7	16.1 - 19.4	1.41	12.5 - 25.0	18.8
11	18	15	14.5	13.2 - 15.8	1.42	10.2 - 20.5	15.3
11	23	15	19.7	18.4 - 21.4	1.31	15.0 - 25.9	20.5
	Last dose October 23						
11	Oct. 24	15	25.5	23.8 - 27.2	1.29	19.6 - 33.0	26.3
12	25	14	21.1	19.6 - 22.7	1.34	16.1 - 27.6	21.8
12	27	14	22.2	20.7 - 23.9	1.32	16.9 - 29.3	23.0
12	29	14	13.0	11.8 - 14.4	1.45	8.9 - 18.9	13.8
13	Nov. 1	14	9.6	8.6 - 10.9	1.50	6.4 - 14.4	10.3
	Dosage resumed November 1						
13	Nov. 4	14	15.5	14.3 - 16.8	1.34	11.5 - 20.8	16.1
13	6	15	15.7	14.5 - 17.1	1.38	11.4 - 21.8	16.5
14	8	15	15.3	14.4 - 16.3	1.28	11.9 - 19.7	15.8
14	11	15	18.5	17.3 - 19.7	1.28	14.4 - 23.6	19.0
14	13	15	17.3	16.3 - 18.8	1.26	13.7 - 21.9	17.8
15	15	15	17.6	16.6 - 18.8	1.27	13.9 - 22.3	18.1
			All Bleedings Group Y				
8	Sept. 27	14	20.1	18.8 - 21.6	1.30	15.5 - 26.2	20.8
8	Oct. 2	14	20.4	18.5 - 22.5	1.45	14.0 - 29.6	21.5
9	4	14	20.7	19.3 - 22.0	1.28	16.2 - 26.4	21.2
9	9	14	19.1	17.9 - 20.3	1.28	14.9 - 24.3	19.6
10	11	14	20.4	19.3 - 21.6	1.23	16.6 - 25.2	20.5
10	16	13	19.2	17.5 - 21.2	1.41	13.7 - 27.1	20.3
11	18	13	14.7	13.9 - 16.0	1.58	10.7 - 20.2	15.4
11	23	14	20.8	19.5 - 22.2	1.27	16.4 - 26.4	21.3
	Last dose October 23						
11	Oct. 24	14	24.3	22.9 - 25.7	1.25	19.5 - 30.2	24.8
12	25	14	22.0	20.5 - 23.0	1.24	17.7 - 27.4	22.5
12	27	13	24.8	23.1 - 26.8	1.31	19.0 - 32.5	25.7
12	29	13	13.5	12.5 - 14.5	1.30	10.4 - 17.5	13.8
13	Nov. 1	14	10.1	9.1 - 11.0	1.42	7.1 - 14.3	10.6
13	4	14	9.9	9.1 - 10.8	1.37	7.2 - 13.7	10.6
13	6	13	5.7	4.9 - 6.5	1.63	3.5 - 9.2	6.3
14	8	14	7.5	6.9 - 8.2	1.40	5.4 - 10.6	7.9
	Dosage resumed November 8						
14	Nov. 11	14	13.0	12.2 - 14.0	1.30	10.1 - 16.7	13.4
14	13	14	14.0	12.9 - 14.5	1.25	11.0 - 17.1	14.0
15	15	14	12.4	11.7 - 13.2	1.26	9.8 - 15.7	12.7

TABLE 10.—*Plasma Quinacrine Levels (Micrograms per Liter) of Group of Men (Company C) Receiving No Drug After Eleven Weeks of Suppressive Dosage*

Week No.	Week Date	Number of Men	$Mean_G$	68% Range of $Mean_G$	Dispersion σ_G	Dispersion 68% Range	Dispersion $Mean_A$
			Company C Section 1				
12	Nov. 13	32	12.8	12.8 - 13.4	1.34	9.5 - 17.1	13.5
12	15	39	9.6	9.0 - 10.1	1.42	6.7 - 12.6	10.2
12	17	39	9.8	8.6 - 9.6	1.42	6.4 - 12.9	9.6
13	20	39	6.3	5.8 - 6.8	1.67	3.8 - 10.5	7.2
			Company C Section 2				
12	Nov. 13	44	17.0	16.3 - 17.8	1.33	12.8 - 22.5	17.6
12	15	45	12.8	12.1 - 13.5	1.41	9.1 - 18.0	13.5
12	17	43	11.8	11.3 - 12.4	1.34	8.9 - 15.8	12.3
13	20	44	10.5	10.0 - 11.0	1.39	7.6 - 14.6	11.1

IV. INDIVIDUAL VARIATION OF PLASMA CONCENTRATION AND PREDICTION OF CONCENTRATION

Individual Variation.—Subjects on the same dosage regimen may differ markedly in their plasma quinacrine concentrations. For example, in a group of 85 men on a regimen of 0.4 Gm. per week the equilibrium plasma quinacrine levels were distributed as shown in chart 13. In order to describe the distribution pattern and the variability of the plasma levels, statistical treatment of the data has been employed. It is immediately evident from the unsymmetric pattern in chart 13 that the variability in plasma levels does not follow the normal arithmetic probability distribution. Therefore the arithmetic mean and the standard deviation, which apply to the normal arithmetic probability curve,

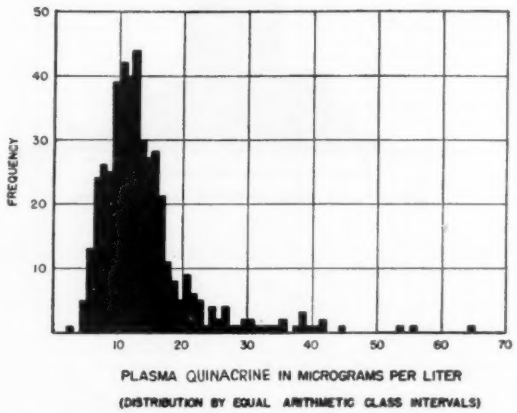


Chart 13.—Frequency distribution of plasma quinacrine levels in Company B, Section 1, seventh through eleventh week.

are not suitable to describe the distribution of the individual plasma quinacrine levels. When the individual variations in the equilibrium plasma quinacrine levels are expressed logarithmically the distribution is approximately symmetric and is found to approach closely a logarithmic probability distribution (chart 14). The normality of the logarithmic distribution is demonstrated by the fact that the cumulative frequency curve plotted on logarithmic probability paper yields an approximately straight line over most of the range (chart 15). This linearity test was applied to every set of group data, and satisfactory straight line plots were obtained in all cases. The few exceptional subjects who exhibited abnormally high quinacrine levels for extended periods were insufficient in number to affect significantly the group values.

The representative value for data which are characterized by a logarithmic probability distribution is the geometric mean, abbreviated to $MEAN_G$. This is the antilog of the arithmetic mean of the logarithms of the observed values and thus differs from the customary arithmetic

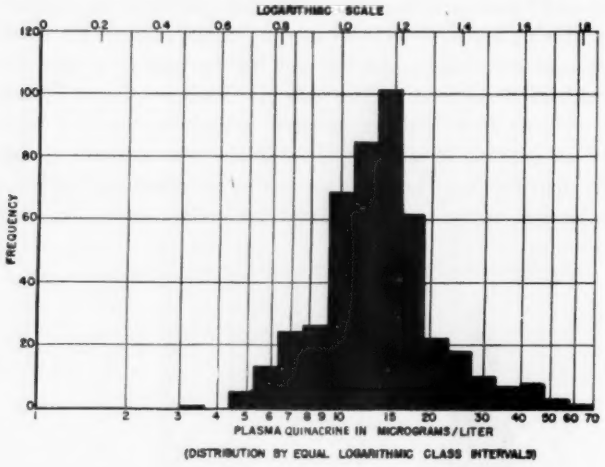


Chart 14.—Frequency distribution of plasma quinacrine levels in Company B, Section 1, seventh through eleventh week.

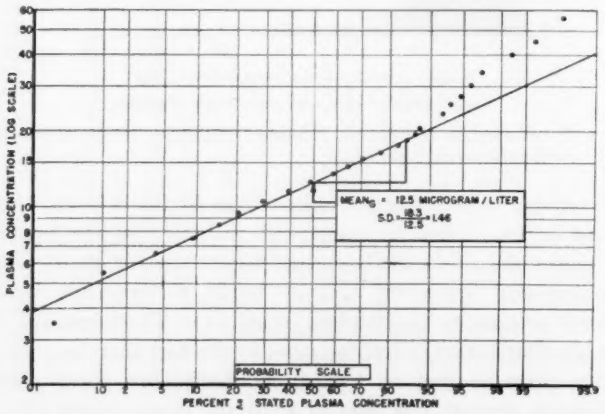

PLASMA CONCENTRATION (LOG SCALE)
MEAN$_G$ = 12.5 MICROGRAM / LITER
S.D. = 18.2 / 12.5 = 1.46
PROBABILITY SCALE
PERCENT ≤ STATED PLASMA CONCENTRATION

Chart 15.—Cumulative percentage distribution of plasma quinacrine levels in Company B, Section 1, seventh through eleventh week.

mean. The dispersion of logarithmically distributed data is measured by the standard geometric deviation rather than by the standard deviation as in arithmetically distributed values. The standard geometric devia-

tion is the antilog of the standard arithmetic deviation of the logarithms of the observed values about the logarithmic mean. As a measure of the dispersion of data the standard geometric deviation differs basically from the common conception of linear dispersion as measured by the arithmetic standard deviation. In a normal arithmetic distribution the probabilities are equal that deviations of plus or minus 1 standard deviation about the mean will occur. With a log-probability distribution, on the other hand, probabilities are equal that deviations obtained by multiplying or dividing the $MEAN_G$ by 1 standard geometric deviation will occur. Thus, in terms of a normal logarithmic probability curve, the relative significance of high and low values becomes quite different from their meaning when viewed in arithmetic relation to the mean.

TABLE 11.—*Predicted Distribution of Individual Plasma Levels in Men on a Given Regimen (Presented as a Cumulative Frequency Distribution of the Individual Plasma Levels, Which Are Expressed as Ratios of the Mean$_G$ of the Group)*

Individual Levels (Factor by Which Mean$_G$ Is to Be Multiplied)	Percentage of Men Having Stated Level or Less
0.4 × Mean$_G$	1
0.5	3
0.6	8
0.7	17
0.8	27
1.0	50
1.2	70
1.4	82
1.6	90
2.0	97
2.5	99

Under the geometric concept, a level of 80 micrograms per liter in a group of data having a geometric mean level of 20 micrograms per liter has the same probability of occurrence as a level of 5 micrograms per liter ($\frac{80}{20} = \frac{20}{5} = 4$), whereas in a normal arithmetic probability distribution with an arithmetic mean of 20, values of 5 would occur with much greater frequency than values of 80. It is not suggested that the geometric distribution is an invariable characteristic of the plasma quinacrine levels of a group. It was, however, repeatedly observed in this study and provided a method for describing the variability of the plasma quinacrine levels which was more representative than the common arithmetic method. The standard geometric deviation was found to be almost constant for all sets of data and varied but little from week to week. Its average value of 1.45 permits one to predict (within the limits of the study) the range and distribution of the individual plasma quinacrine levels in a group of men subjected to a given suppressive regimen (table 11).

The dispersion of individual values by 1 standard geometric deviation (68 per cent range) about the geometric mean is shown graphically in charts 3 and 4. The values included within a range of 1 standard geometric deviation on either side of the $MEAN_G$ are also listed in the tables. From these values and the standard error of the means the $MEAN_G$ are shown to be highly stable.

Not evident in either the charts or the tables is the wide variance of certain subjects whose plasma levels fell outside the 68 per cent range. These men were characterized by either consistently low or consistently high values. The high values resulted from a sudden departure from previous levels which, though declining somewhat thereafter, remained elevated above the remainder of the group. In view of the small sample studied, the validity of special consideration for the small numbers of subjects who lie at the extremes may be questioned, since the sample was insufficient to make certain that only one universe was under study. One assumes, nonetheless, that with a sufficiently large sample the discontinuity would be eliminated. The characteristics of the groups at the extremes are worthy of discussion, since they illustrate types of behavior which may be of practical importance from the standpoint of suppressive therapy.

Approximately 7 per cent of both the men receiving 0.4 Gm. per week and the men receiving 0.6 Gm. per week showed unusually low levels for their respective groups. These men reached their equilibrium values earlier than the group as a whole and maintained consistently low levels. This was apparently a characteristic of the individual response to the drug. The low values were not the result of failure to take the drug or of lack of solution of the tablet in the intestine, for the administration of quinacrine in solution produced no change in plasma values.

Another 7 per cent of both the subjects receiving 0.4 Gm. per week and the subjects receiving 0.6 Gm. per week exhibited a more or less sudden departure from previous plasma levels to exceptionally high ones. This rise to unusually high levels was irregular in appearance, occurring at various times between the third and eighth weeks. After the new high level had been reached the behavior varied. In the main there followed a gradual decline to a new level which, nevertheless, was significantly higher than either the level before the sudden rise or the level for the group. These sporadic increases in plasma level were not associated with clinical evidence of toxicity nor with evidence of associated hepatic damage. Typical curves of plasma quinacrine levels illustrating the responses of men with unusually high or unusually low levels are presented in chart 16.

The wide dispersion of values about the mean is a matter of considerable practical importance in any consideration of the degree of

protection afforded a population by any standard dosage regimen. From the point of view of characterizing the population as a whole, the mean and the standard deviation are useful tools. From the point of view of protection of troops in the field, however, it is the status of that portion of the group with the lowest plasma levels which is a matter of concern,

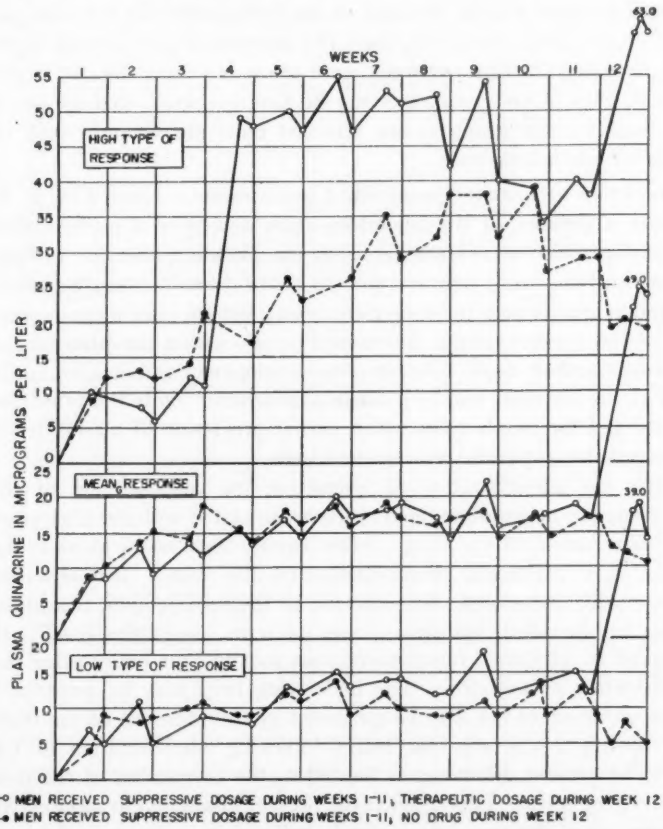

WEEKS
1 2 3 4 5 6 7 8 9 10 11 12
HIGH TYPE OF RESPONSE
MEAN RESPONSE
LOW TYPE OF RESPONSE
PLASMA QUINACRINE IN MICROGRAMS PER LITER
43.0
49.0
39.0
MEN RECEIVED SUPPRESSIVE DOSAGE DURING WEEKS 1-11, THERAPEUTIC DOSAGE DURING WEEK 12
MEN RECEIVED SUPPRESSIVE DOSAGE DURING WEEKS 1-11, NO DRUG DURING WEEK 12

Chart 16.—Differences in plasma quinacrine levels of persons receiving 0.6 Gm. per week.

since it may be assumed, granting the premise that the effectiveness of the drug is a function of the plasma level, that this fraction of the group has the least protection and will manifest the highest malaria attack rate. With this in mind the population may be examined during the different weeks of suppressive dosage to determine what per cent of the total exceeds or fails to achieve any arbitrarily selected plasma level. In charts 17 and 18 the distribution of plasma quinacrine levels

in each week is plotted as a single curve. These are smoothed probability curves obtained from the calculated geometric means and standard geometric deviations of the data.[8] They represent the most probable prediction curves which emerge from the present study. If, for example, a level of 10 micrograms per liter is desired, one finds that at equilibrium (weeks 7 through 11) 37 per cent of the group receiving 0.4 Gm. per week failed to reach this level (chart 17) whereas only 7 per cent of the group receiving 0.6 Gm. per week were below it (chart 18). It is also apparent, even in the group receiving 0.6 Gm. per week, that the maximum level for the group is not achieved until the seventh week of quinacrine administration.

Prediction of Plasma Quinacrine Concentration.—Lieut. Col. F. S. Brackett, a member of the laboratory staff, developed a mathematical relationship which accurately describes the plasma quinacrine concentration as a function of time and amount of the dose. This mathematical description applies only to group mean levels, but for such means agrees with all the experimentally determined points within the precision of the analytic technic used. The complete development and detailed application of the formulas will be published elsewhere.[6] Only the principles involved and the simple rules which permit prediction of plasma levels for suppressive regimens are discussed here.

After the administration of quinacrine the concentration of the drug in the plasma exhibits rapid changes associated with the absorption and redistribution of the drug. After twenty-four hours these initial changes have practically disappeared, and the values then observed can be readily correlated. As indicated in the introduction, the initial changes will be called "transients," and the term "underlying level" will be applied to all values found more than twenty-four hours after the administration of any dose. The underlying level may be considered to exist at all times but may be concealed by the presence of the transients during the twenty-four hours following administration of the drug. The present discussion is limited to the correlation of the data on underlying levels. This restricts the present discussion to suppressive regimens, since the transients must be taken into account in the prediction of levels for a therapeutic regimen where the doses are administered at intervals of less than a day.[9]

8. The curve for week 4 (chart 18) was incongruous and has been omitted. Data from which it was derived are unreliable because abnormally high results were obtained for all samples on this day.

9. The transient phenomena are subject to mathematical description as satisfactory as that briefly given here for the underlying levels. The complete development of this aspect of the study and its application to prediction of levels encountered on therapeutic regimens will be described elsewhere.[6]

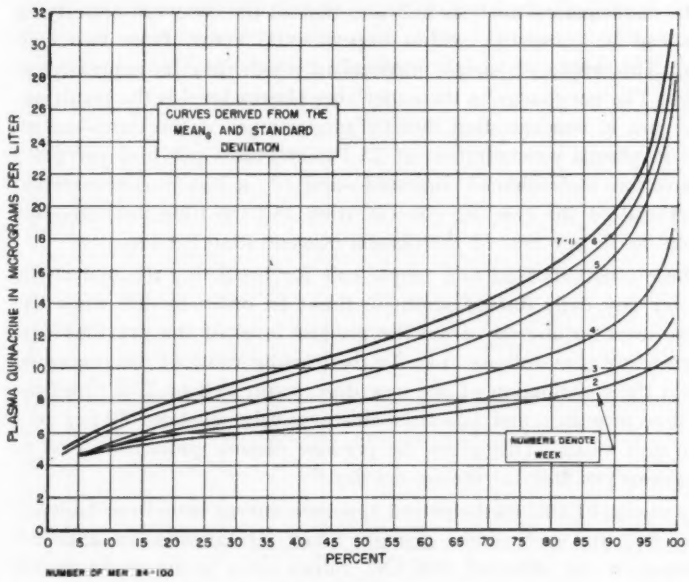


Chart 17.—Cumulative frequencies of minimum weekly plasma quinacrine levels of groups of men (ARTC Companies B and C) receiving 0.4 Gm. per week.

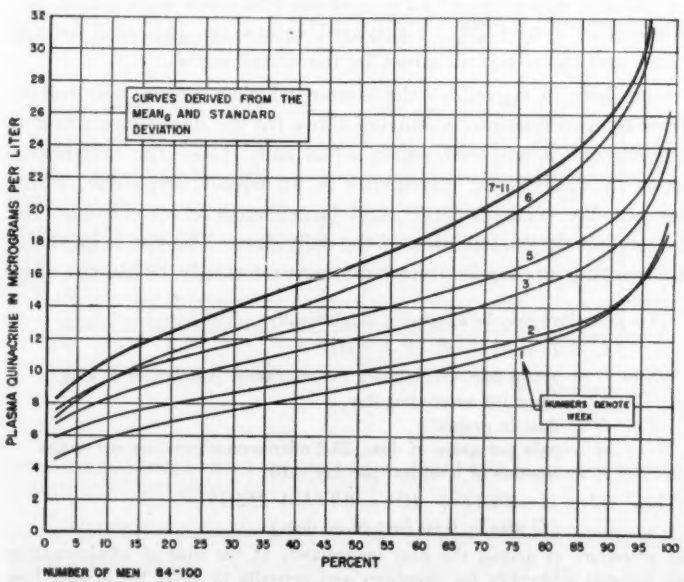


Chart 18.—Cumulative frequencies of minimum weekly plasma quinacrine levels of groups of men (ARTC Companies B and C) receiving 0.6 Gm. per week.

The mathematical analysis indicates that all the observed underlying values can be computed, within experimental error, from two constants. This implies a simple mechanism which may be expressed as follows: The net change in the underlying plasma level is the result of: (1) a gain in concentration directly proportional to the dose—an increase in plasma concentration of 23.2 micrograms per liter per gram of quinacrine hydrochloride ingested—and (2) a loss in concentration proportional to the existing concentration and the time interval—this amounts to 10 per cent of the plasma concentration per day.

These constants lead to a simple rule for predicting the underlying level for any daily dosage regimen, thus: In order to determine the predose level on any day from the predose level of the previous day, the procedure is as follows: (1) To the predose value of the preceding day add the contribution of the new dose, expressed by 23.2 times the daily dose in grams, and (2) from this new value subtract 10 per cent of the new value. This gives the predose plasma quinacrine level in micrograms per liter for the second day.[10]

By means of this mathematical approach curves have been built up, day by day, for each of the groups. Chart 19 indicates the excellent agreement of the observed $MEAN_G$ values for a group of 84 to 100 men with the theoretically computed values for the group over a period of eighty-five days. Similar agreement is evident in the values for a group of 30 men who received 1.2 Gm. in the first week and 0.6 Gm. per week thereafter (chart 20). Calculated values are indicated by the solid curve and the observed values by the dotted curve.

Certain facts in regard to the course which a group will follow arise from the two relations postulated above for the simple mechanisms. When quinacrine is administered in equal daily doses, the underlying level rises by diminishing increments to an equilibrium value, while the loss per day becomes larger and larger until at equilibrium the daily loss equals the contribution of the daily dose. The rise is logarithmic, approaching the equilibrium value asymptotically. This rise may

10. This procedure may be expressed algebraically:

$$L' = L + AD - K\,(L + AD)$$

Where L = group $MEAN_G$ plasma concentration just before a dose.
L' = same for succeeding day.
D = dose in grams.
A = gain per gram of dose, 23.2 micrograms per liter per gram.
K = fraction of level lost per day, 0.10.

Then $L' = (1-K)\,(L + AD) = 0.9\,(L + 23.2D)$
(D may be 0 on days of no dose)

The procedure of adding the gain immediately at the time of administration has been adopted arbitrarily for simplicity and partially to offset the greater loss arising from transient elevation of level.

be described as follows: The increase in level per day is 10 per cent of the difference between the daily level and the equilibrium level. Therefore 50 per cent of the rise takes place in one week, 75 per cent

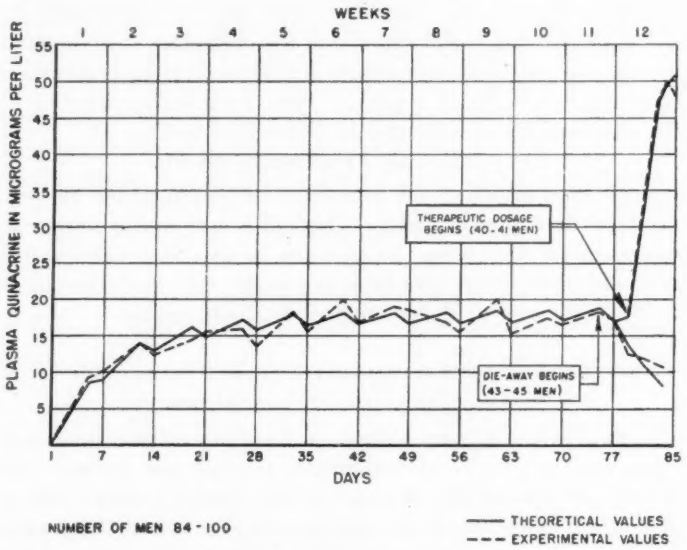

WEEKS
1 2 3 4 5 6 7 8 9 10 11 12
PLASMA QUINACRINE IN MICROGRAMS PER LITER
55 50 45 40 35 30 25 20 15 10 5
THERAPEUTIC DOSAGE BEGINS (40-41 MEN)
DIE-AWAY BEGINS (43-45 MEN)
1 7 14 21 28 35 42 49 56 63 70 77 85
DAYS
NUMBER OF MEN 84-100
THEORETICAL VALUES
EXPERIMENTAL VALUES

Chart 19.—Comparison of theoretic and experimental MEAN$_0$ plasma quinacrine levels for a dosage schedule of 0.6 Gm. per week.

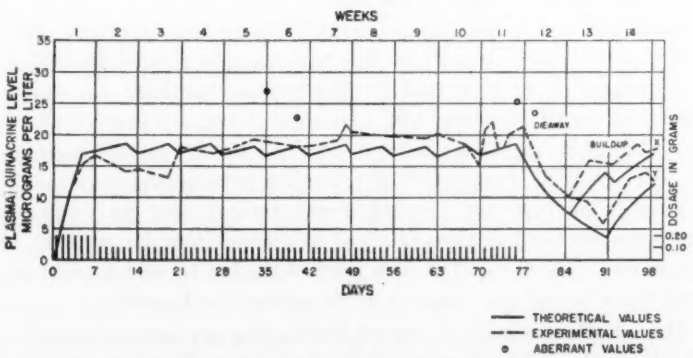

WEEKS
1 2 3 4 5 6 7 8 9 10 11 12 13 14
PLASMA QUINACRINE LEVEL MICROGRAMS PER LITER
35 30 25 20 15 10 5 0
DIE-AWAY
BUILDUP
DOSAGE IN GRAMS
0.20
0.10
0 7 14 21 28 35 42 49 56 63 70 77 84 91 98
DAYS
THEORETICAL VALUES
EXPERIMENTAL VALUES
ABERRANT VALUES

Chart 20.—Comparison of theoretic and experimental plasma quinacrine levels for a dosage schedule of 1.2 Gm. the first week and 0.6 Gm. every subsequent week (experimental curve based on the results for 30 men).

by the end of the second week, 87 per cent by the end of the third, etc. By the end of the sixth week 98 per cent of the rise to equilibrium level has taken place, and only 2 per cent of the total rise remains.

As a necessary consequence of this description the equilibrium value is proportional to the dose. Thus, for equilibrium (gain = loss): The level can be shown to be equal to $23.2\ (\frac{1}{K} - 1)\ D$ or $23.2 \times 9D$, hence $209D$ where D is the daily dose. This direct proportionality between the equilibrium concentration and the daily dose is of practical importance, since it provides a means for predicting the maintenance level achieved by any dosage regimen. Thus, for a daily quinacrine intake of 0.15 Gm., the underlying equilibrium level will be:

$$209 \times 0.15 = 31.3 \text{ micrograms per liter}$$

After discontinuance of the administration of quinacrine the level will fall logarithmically (chart 12). This fall is very similar to the rise, 10 per cent of the level being lost each day, so that 50 per cent will be lost after one week, 75 per cent after two weeks, etc. At the end of six weeks only 2 per cent of the equilibrium level will remain.

V. THE INFLUENCE OF SIMULATED JUNGLE CLIMATE ON PLASMA QUINACRINE CONCENTRATION

Procedure.—The 30 men utilized in this phase of the study were subjected to three weeks of preliminary training and testing, after which they were divided into two equal groups (jungle groups A and B) which were comparable in weight, age and physical fitness. Each group was handled in exactly the same manner except for climatic exposure. One group was initially moved into the laboratory hot room, while the other remained in barracks on the post.

In the hot room a hot humid (jungle) climate was simulated. During the day (8 a.m. to 5 p.m.) the dry bulb temperature averaged 90 F., with extremes of 89 F. to 93.5 F. The relative humidity was usually 92 per cent to 95 per cent, with extremes of 100 per cent to 88 per cent. During the night (6 p.m. to 6:30 a.m.) the dry bulb temperature was 78 F. to 87 F. (usually 84 F.), and the relative humidity was 75 per cent to 85 per cent. No additional radiant heat was supplied. Approximately one hour was required to change from day to night, or night to day, conditions. The men lived in the hot room day and night except for a ten minute clean-up in the morning and evening.

The outside environment varied from a hot dry summer period to cool fall weather. This climate is indicated in chart 21, which shows the dry bulb temperature and relative humidity as the average values for all readings during each work period throughout the week. The hot humid climate is similarly plotted on the same chart. Psychrometric readings were taken every fifteen minutes during the working periods both inside the hot room and out of doors.

Both groups were subjected to a daily standard work procedure consisting of five work periods. Each work period consisted of a march of 2½ miles (4 kilometers) in forty-seven minutes. Each man carried a 20 pound (9 Kg.) pack. Between successive work periods there were thirteen minutes of rest, during which observations were made on the men. Two successive work periods in the morning and three in the afternoon (a total walk of 12½ miles [20 kilometers]) constituted a standard work day. Five work periods daily on the first five days of the week, three periods on Saturday and none on Sunday constituted the standard work week. One hour periods of organized athletics, calisthenics or close order drill were at times substituted for work periods in the outside group.

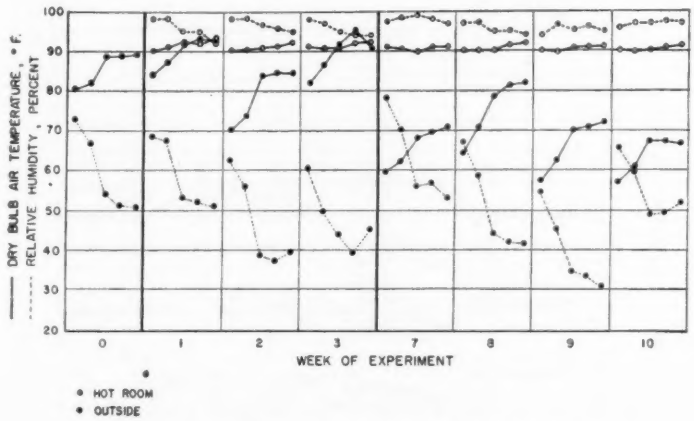


Chart 21.—Climatic conditions during work hours.

During the work periods all men wore the regulation fatigue coverall, cotton shorts, socks and shoes. The food consisted of standard garrison rations and was salted to individual taste. During work, water salted to a final concentration of 0.1 per cent was drunk as desired. This was the only water permitted in the hot room at any time. The group outside drank salted water during the work periods and fresh water at other times. Approximately eight to nine hours were allowed for sleep.

Suppressive quinacrine dosage was begun in both groups on the day that the first group entered the hot room. During six days of the first week each man received 0.1 Gm. with his morning and evening meals, a total of 1.2 Gm. per week. During the following ten weeks each man received 0.6 Gm. per week, 0.1 Gm. daily for six days.

After preliminary training for all subjects, group A entered the hot room while group B remained in the outside summer climate. The men in group A were permitted to leave the hot room from 1 p.m. each Saturday until 10 p.m. Sunday. After seven weeks group A moved outside and group B entered the hot room. For the next four

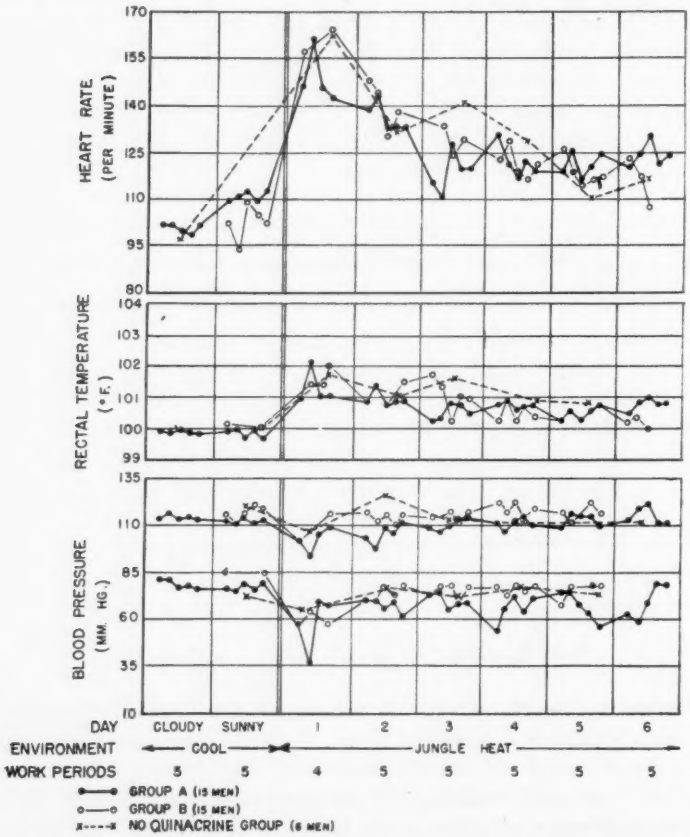


Chart 22.—Changes in heart rate, rectal temperature and blood pressure during acclimatization to work in jungle heat.

weeks group B remained continuously in this environment; they were not permitted to leave on Saturday afternoon and Sunday.

Before and after each work period the following observations were made: *(a)* general appearance and symptoms, *(b)* heart rate and blood pressure in both erect and supine positions and *(c)* rectal temperature. The weight (sweat) loss, within 10 Gm., was determined for each work

period. Measurements of the twenty-four hour water intake and urine output were made daily on the subjects in the hot room.

TABLE 12.—*Mean$_G$ and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Jungle Group A (Receiving 0.6 Gm. per Week)*

Week No.	Week Date	Number of Men	Mean$_G$	68% Range of Mean$_G$	Dispersion σ_G	Dispersion 68% Range	Mean$_A$
			Bleeding H_1				
1	Aug. 12	15	11.6	11.0 - 12.1	1.21	12.1 - 13.9	11.8
2	16	15	18.2	17.5 - 19.0	1.17	15.6 - 21.3	18.4
3	23	15	14.6	13.9 - 15.4	1.22	11.9 - 17.8	15.0
4	30	15	18.7	18.0 - 19.4	1.15	16.2 - 21.5	19.0
5	Sept. 6	15	19.7	18.2 - 21.5	1.39	14.2 - 27.4	20.9
6	13	15	28.6	26.0 - 31.5	1.45	19.8 - 41.4	30.7
7	20	14	16.0	14.5 - 17.7	1.46	11.0 - 23.4	20.1
8	27	15	20.1	18.0 - 22.5	1.55	13.0 - 31.2	23.1
9	Oct. 4	15	19.1	17.4 - 21.0	1.44	13.2 - 27.5	20.6
10	11	15	19.3	17.9 - 20.8	1.34	14.4 - 25.8	20.2
11	18	15	15.2	13.9 - 16.7	1.42	10.8 - 21.5	15.5
12	25	14	20.6	19.0 - 22.2	1.33	15.4 - 27.1	21.4
			Bleeding H_2				
1	Aug. 14	15	16.2	15.4 - 17.0	1.21	13.3 - 19.6	16.4
2	21	14	14.3	13.7 - 15.0	1.18	12.2 - 16.9	14.5
3	28	15	13.6	12.9 - 14.4	1.25	10.9 - 17.1	13.9
4	Sept. 4	15	17.7	16.2 - 19.2	1.39	12.7 - 24.6	18.6
5	11	15	19.4	18.1 - 20.8	1.48	13.1 - 28.8	21.1
6	18	15	21.4	19.6 - 23.3	1.40	15.3 - 30.0	23.9
7	25	15	17.9	16.1 - 19.9	1.49	12.0 - 26.8	19.5
7	26	15	20.8	19.1 - 22.9	1.42	14.7 - 29.7	22.3
8	Oct. 2	15	19.2	17.1 - 21.6	1.57	12.3 - 30.1	21.1
9	9	15	20.7	19.5 - 22.0	1.42	14.5 - 30.1	22.0
10	16	15	21.3	19.6 - 23.1	1.38	15.4 - 29.4	22.7
11	19	14	20.1	18.8 - 21.5	1.29	15.6 - 25.8	20.7
11	20	14	22.1	20.1 - 24.3	1.42	15.5 - 31.5	23.6
11	21	14	18.0	16.4 - 19.7	1.41	12.7 - 25.3	19.1
11	22	14	18.2	16.8 - 19.8	1.37	13.3 - 24.9	19.0
11	23	14	21.2	19.7 - 22.8	1.31	16.1 - 27.9	22.0
11	24	14	24.4	22.7 - 26.1	1.30	18.7 - 31.8	25.2
12	27	14	21.4	19.9 - 23.0	1.31	16.4 - 28.0	22.1
12	29	13	12.7	11.4 - 14.1	1.47	8.7 - 18.6	13.5
13	Nov. 1	14	8.7	7.9 - 9.6	1.42	6.1 - 12.3	9.2
			Bleeding H_{2+5}				
1	Aug. 14	15	25.2	23.9 - 26.6	1.23	20.6 - 30.9	25.7
2	21	15	22.6	21.8 - 23.4	1.15	19.6 - 26.0	22.8
3	28	15	20.8	19.7 - 21.8	1.23	16.9 - 25.4	21.3
4	Sept. 4	15	26.7	25.2 - 28.4	1.26	21.3 - 33.6	27.5
5	11	15	34.8	32.3 - 37.6	1.34	26.0 - 46.7	36.4
6	18	15	36.6	33.7 - 39.8	1.37	26.7 - 50.4	38.7
8	Oct. 2	15	28.1	26.1 - 30.2	1.33	21.0 - 37.3	29.3
9	9	15	22.8	21.0 - 27.7	1.37	16.6 - 31.2	23.9
10	16	14	24.0	22.1 - 26.2	1.38	17.4 - 33.2	25.2

Blood samples for plasma quinacrine were taken three times each week (*a*) H_1 at 11:15 a.m. Monday, approximately fifty-four hours after the last preceding dose; (*b*) H_2 at 6:30 a.m. Saturday, eighteen

hours after the last preceding dose, and (*c*) H_{2+5} at 11:30 a.m. Saturday, five hours after the last dose of quinacrine of the week. Blood samples were always obtained from both groups at the same time.

TABLE 13.—*Mean$_G$ and Characteristics of Weekly Plasma Quinacrine Levels (Micrograms per Liter) for Jungle Group B (Receiving 0.6 Gm. per Week)*

Week		Number of Men	Mean$_G$	68% Range of Mean$_G$	Dispersion		
No.	Date				σ_G	68% Range	Mean$_A$
			Bleeding H_1				
1	Aug. 12	15	11.2	10.5 - 12.1	1.32	8.5 - 14.8	11.6
2	16	14	16.1	15.2 - 17.1	1.25	12.9 - 20.2	16.5
3	23	15	14.9	14.4 - 15.4	1.13	13.1 - 16.9	15.0
4	30	14	17.9	17.3 - 18.6	1.23	14.6 - 22.0	18.2
5	Sept. 6	15	15.7	14.6 - 17.0	1.38	11.7 - 21.2	16.5
6	15	15	25.2	23.7 - 26.6	1.08	19.8 - 32.0	25.8
7	20	15	20.4	18.7 - 22.2	1.39	14.7 - 28.2	21.3
8	27	14	21.6	20.3 - 23.1	1.27	17.1 - 27.4	22.2
9	Oct. 4	15	21.1	19.8 - 22.5	1.28	16.4 - 27.1	21.7
10	11	15	21.4	20.1 - 22.9	1.30	16.4 - 28.0	22.3
11	18	14	14.6	13.6 - 15.7	1.30	11.2 - 19.1	15.0
12	25	14	26.6	21.5 - 23.8	1.21	18.6 - 27.4	23.0
			Bleeding H_2				
1	Aug. 14	15	16.0	15.1 - 17.0	1.26	12.7 - 20.2	16.4
3	21	14	14.3	13.7 - 14.9	1.16	12.3 - 16.6	14.4
3	28	15	13.4	12.6 - 14.2	1.26	10.6 - 16.9	13.7
4	Sept. 4	15	16.6	14.9 - 18.4	1.50	11.0 - 24.9	16.8
5	11	15	19.6	18.5 - 20.9	1.27	15.5 - 25.0	20.2
6	18	15	24.0	22.5 - 25.7	1.29	18.7 - 30.9	24.7
7	25	15	21.0	19.3 - 22.9	1.39	15.1 - 29.3	22.1
7	26	15	21.5	19.9 - 23.3	1.36	15.9 - 29.2	22.5
8	Oct. 2	15	21.2	19.9 - 22.5	1.27	16.6 - 26.9	21.7
9	9	14	18.4	17.2 - 19.7	1.28	14.3 - 23.6	18.9
10	16	13	15.6	14.5 - 16.8	1.31	11.9 - 20.4	16.2
11	19	15	22.2	21.0 - 23.3	1.22	18.1 - 27.1	22.6
11	20	15	22.6	21.3 - 23.9	1.25	18.0 - 28.2	23.1
11	21	15	19.1	18.1 - 20.2	1.23	15.5 - 23.5	19.5
11	22	15	17.8	16.4 - 19.3	1.35	13.0 - 24.3	22.1
11	23	15	19.4	18.3 - 20.6	1.27	15.4 - 24.6	19.9
11	24	15	26.0	24.5 - 27.5	1.25	20.8 - 32.4	26.5
12	27	13	25.9	24.1 - 27.8	1.29	20.0 - 33.5	26.6
12	29	14	13.7	12.8 - 14.6	1.28	10.7 - 17.5	14.1
13	Nov. 1	14	11.1	10.1 - 12.2	1.44	7.7 - 16.0	11.7
			Bleeding H_{2+5}				
1	Aug. 14	15	25.6	24.3 - 26.9	1.22	21.0 - 31.1	26.1
2	21	15	20.1	19.4 - 20.7	1.14	17.6 - 22.8	20.2
3	28	15	19.2	18.4 - 20.0	1.17	16.4 - 22.4	19.4
4	Sept. 4	15	24.2	23.2 - 25.2	1.17	20.7 - 28.2	24.5
5	11	14	29.7	28.5 - 31.0	1.17	25.4 - 34.7	30.4
6	18	15	33.5	31.2 - 35.9	1.31	25.6 - 43.8	34.6
8	Oct. 2	15	26.8	25.0 - 28.6	1.30	20.6 - 34.8	27.6
9	9	10	22.7	21.9 - 24.1	1.21	18.8 - 27.5	23.1
10	16	15	22.3	21.3 - 23.3	1.19	18.8 - 26.5	22.7

Results.—In chart 22 are compared the work performance and rate of acclimatization in humid heat of three groups of men: (*a*) group A,

men receiving quinacrine daily simultaneously with entry into the hot environment; *(b)* group B, men who had received quinacrine for seven weeks before exposure to the hot environment, and *(c)* a control group

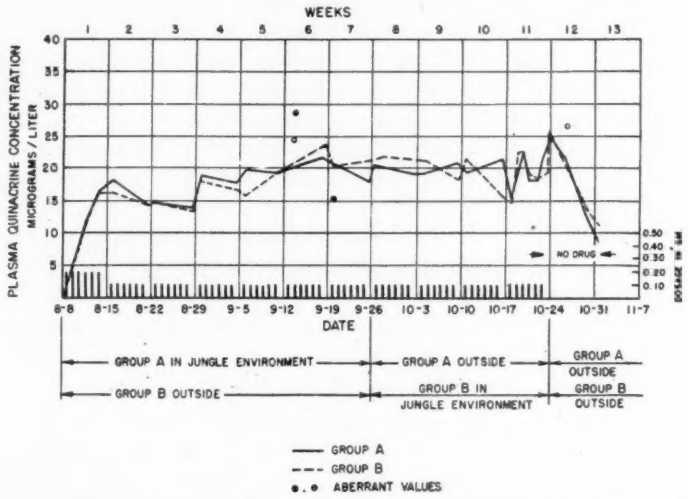

WEEKS
1 2 3 4 5 6 7 8 9 10 11 12 13
PLASMA QUINACRINE CONCENTRATION MICROGRAMS / LITER
40 35 30 25 20 15 10 5
0.50 0.40 0.30 0.20 0.10
MG. IN 250 CC.
NO DRUG
8-8 8-15 8-22 8-29 9-5 9-12 9-19 9-26 10-3 10-10 10-17 10-24 10-31 11-7
DATE
GROUP A IN JUNGLE ENVIRONMENT
GROUP A OUTSIDE
GROUP A OUTSIDE
GROUP B OUTSIDE
GROUP B IN JUNGLE ENVIRONMENT
GROUP B OUTSIDE
GROUP A
GROUP B
ABERRANT VALUES

Chart 23.—MEAN$_0$ plasma quinacrine concentrations of jungle groups A and B.

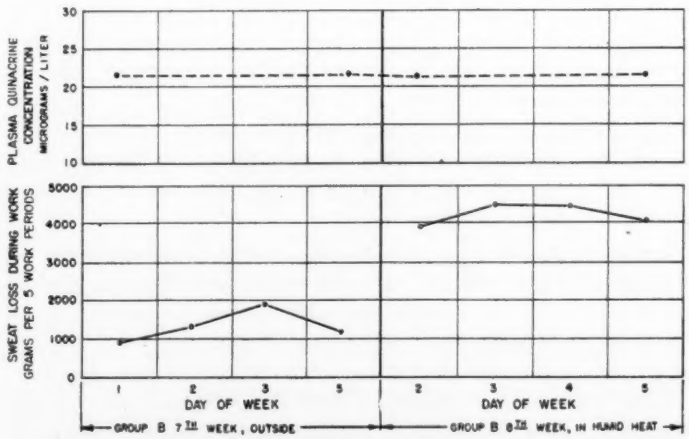

PLASMA QUINACRINE CONCENTRATION MICROGRAMS / LITER
30 25 20 15 10
SWEAT LOSS DURING WORK GRAMS PER 5 WORK PERIODS
5000 4000 3000 2000 1000 0
1 2 3 5
DAY OF WEEK
2 3 4 5
DAY OF WEEK
GROUP B 7TH WEEK, OUTSIDE
GROUP B 8TH WEEK, IN HUMID HEAT

Chart 24.—High rate of sweat loss in humid heat does not affect plasma quinacrine concentration.

of 6 men who received no quinacrine at any time. The performance on the first day and thereafter and the progress of acclimatization in the three groups of subjects did not differ in any significant way from

that observed in previously reported studies of the effect of moist heat on the performance of men.[11] With or without quinacrine the rate of acclimatization and ability to work in a jungle climate were the same.

As shown in chart 23 there was no difference in the rate of increase of the plasma quinacrine concentration or in the final equilibrium levels attained in groups A and B, nor was there a significant change in the equilibrium level in either group when the subjects were shifted from one environment to the other (group data tabulated in tables 12 and 13). The increased rate of sweating experienced by the men in the hot humid environment had no effect on the plasma quinacrine level (chart 24).

The equilibrium levels attained by these two groups (A and B) and the levels reached by the larger ARTC group on the same weekly maintenance dosage did not differ significantly from the level of 18 micrograms per liter predicted for this dosage schedule, the deviations being

TABLE 14.—*Equilibrium Quinacrine Level on Dosage of 0.6 Gm. per Week; Mean$_G$ and Dispersion of Levels*

Exposure	No. of Results	No. of Men	Levels Seventh Through Eleventh Weeks		
			Mean$_G$	S. E. of Mean$_G$	Std. Geom. Deviation
Outside, ARTC group	858	85	17.2	1.04	1.44
7 wks. hot room, 4 wks. outside, group A	205	15	19.9	1.17	1.41
7 wks. outside, 4 wks. hot room, group B	205	15	19.9	1.08	1.32

approximately equivalent to one standard error of the mean. This is apparent in table 14.

The mean levels and the degree of individual variability as measured by the standard deviations are approximately the same for the three groups. Both groups A and B had men with unusually low and unusually high levels.

It is concluded, therefore, that the hot, humid environment has no effect on the absorption and storage of quinacrine and that the required dosage schedule for effective plasma quinacrine concentration is not influenced by the climatic conditions here studied.

VI. THE TOXICITY OF QUINACRINE

There were no toxic reactions attributable to quinacrine in any of the 250 men on any of the suppressive dosage regimens. The health and well-being of all the men were excellent throughout. The ARTC group

11. Eichna, L. W.; Bean, W. B.; Ashe, W. F., and Nelson, N.: Bull. Johns Hopkins Hosp. **76**:25, 1945; Armored Medical Research Laboratory Report on Project 2 (2-7, 11, 13, 15, 17, 19), Oct. 18, 1943.

gained in weight an average of 3 pounds (1.3 Kg.) during the experimental period. Visits to the dispensary by all men in the study were carefully checked. In no instance could the complaints be attributed to quinacrine, nor was the frequency of visits by members of the experimental groups greater than that of other men in the same unit who were not taking the drug.

One instance of probable toxic reaction from quinacrine in therapeutic doses was encountered. This subject had an epileptiform seizure on the fifth day of therapeutic dosage. He had never had a previous seizure, and he had manifested no disturbance while taking suppressive doses. On the day following the seizure his plasma quinacrine level was 108 micrograms per liter, the highest attained by any subject on the therapeutic regimen. Forty-eight hours after the seizure the plasma level had fallen to 67 micrograms. The administration of the drug was continued throughout the seven day regimen, and no further incident occurred. The groups exposed to the hot humid environment remained well throughout.

In view of the frequent reports of quinacrine toxicity the failure to encounter toxic manifestations during the suppressive dosage regimens of the present study is of interest. The subjects of this study differed from men in combat theaters in the absence of the psychologic stresses of combat. In the presence of such stresses one may properly question whether the drug when administered in accordance with the schedule recommended can be considered solely responsible for the reported complaints.

The characteristic yellow discoloration from the drug was noticeable by the end of the first month and increased progressively thereafter. Neither the intensity of this color nor the fluorescence of skin and nails under ultraviolet light correlated with the plasma quinacrine levels.

SUMMARY

1. *Absorption of Quinacrine Following a Single Dose.*—After oral ingestion of quinacrine hydrochloride (atabrine) the plasma level rises rapidly. The major portion of this rise occurs in two hours, and the peak is reached within eight hours. The decrease is rapid at first but becomes progressively slower. By the end of twenty-four hours the rate of fall has assumed a uniform rate proportional to the plasma level. The form of this postabsorption curve changes with continued intake.

2. *Build-Up of Plasma Quinacrine Concentration.*—On a given dosage regimen the plasma concentration increases rapidly during the first week and then more slowly as equilibrium is approached. At the end of the first week approximately one half of the final equilibrium level is attained, at the end of the second week three fourths of the equilib-

rium level, at the end of the third week 87 per cent, at the end of the fourth week 94 per cent and so on, each week halving the remaining difference, so that by the end of the sixth week no perceptible difference from the equilibrium level is observed.

3. *Equilibrium Level Attained in Relation to Dosage Regimen.*—At equilibrium the average plasma quinacrine concentration depends on the total weekly dose and is directly proportional to this dose. Thus for the two regimens, 0.4 Gm. per week and 0.6 Gm. per week, the group mean equilibrium levels attained were 12 and 17 micrograms per liter respectively. In view of this direct proportionality it is possible, within the general limits of the study, to predict the equilibrium plasma level for other dosage regimens. The relationship is : 30 micrograms per liter for 1 Gm. weekly dose.

4. *Effect of Large Initial Doses on the Time Required to Reach Maintenance Levels.*—On a regular regimen of quinacrine intake, from four to six weeks are required to attain the final equilibrium levels. Since half equilibrium values are reached with any regimen in one week, doubling the maintenance dosage for a first week will produce at the end of this time the same level as the equilibrium level of the maintenance dose. This avoids from three to five weeks of delay.

5. *Plasma Levels Attained with the Therapeutic Dosage Schedule.*—Individuals within a group roughly tend to maintain the same distribution of levels on a therapeutic regimen as they exhibited on a suppressive regimen. However, the correlation is not high. The increase of plasma concentration with the institution of a therapeutic regimen after the establishment of equilibrium under a suppressive dosage schedule is functionally related to the time and amount of dose in the same way as at lower and slower rates of intake.

6. *Decrease of Plasma Quinacrine Concentration After Discontinuing the Drug.*—When the drug is discontinued after the establishment of equilibrium levels, the plasma quinacrine concentration decreases in a manner similar to the initial build-up. Thus, 10 per cent of the remaining level is lost each day, and at the end of a week the level will have dropped to half the equilibrium value, to one fourth in two weeks, one eighth in three weeks and so on, each week halving the remaining concentration.

7. *Individual Variability.*—The difference between plasma levels in different individuals may be great. This variability follows a regular pattern and is consistent with the type of statistical analysis (geometric) to which the data have been subjected.

8. *Effect of Climatic Environment on Equilibrium Level.*—In a hot humid environment producing copious sweating the course of build-up and the equilibrium level attained with a given regimen of quinacrine

were the same as those with the same dosage schedule in a temperate climate. Climate had no influence on the equilibrium plasma quinacrine level.

9. *Toxicity.*—There were no toxic reactions from quinacrine in any of the subjects on the various suppressive regimens. One instance of probable reaction to therapeutic dosage occurred.

The following enlisted technicians assisted in these studies: Corporal Alexander Adler, Technician Third Grade Ralph J. Bloom, Sergeant Walter C. Davies, Technician Third Grade Kenneth C. Davis, Sergeant Ernesto Ferrer Jr., Technical Sergeant Eli Gold, Technical Sergeant John L. Gray, Technician Fourth Grade Wayland James, Sergeant Melvin H. Kaplan, Technician Third Grade Arthur Kunes, Technician Fourth Grade Alvin Lieberman, Technician Fourth Grade Guy Millikan, Technician Third Grade Max E. Ress, Technician Third Grade Edward M. Shottick, Master Sergeant Theodore C. Swigert and Technician Fourth Grade Felix Urbush.

Progress in Internal Medicine

ALLERGY

A Review of the Literature of 1944 and 1945, with Comments on Future Problems

FRANCIS M. RACKEMANN, M.D.
Lecturer in Medicine, Harvard Medical School; Physician, Massachusetts General Hospital
BOSTON

(Concluded from Page 718)

HAY FEVER

There are two parts to the treatment of hay fever. One concerns the choice of the particular extract to be used in treatment; the other concerns the technic of doses.

The choice of extracts is important, and, as usual, it is the history which gives the best clue. Skin tests are always interesting, but when one can demonstrate many skin tests with positive reactions that have no symptoms to go with them and then can find clinical evidence of sensitiveness in spite of skin tests with negative reactions one learns to recognize the limitations of the method.

Around Boston, for example, one can distinguish two varieties of what used to be called the typical ragweed history. In one group of patients, the symptoms of hay fever begin around the middle of August, the peak of symptoms is near the first of September and then the symptoms subside, to leave the patient quite clear by about September 20. In the other group of cases the onset is a little earlier, perhaps toward the middle of August, and then the symptoms persist, to recur in paroxysms through October. This type of hay fever comes later than the type caused by ragweed. Patients who give that history often have positive cutaneous reactions to molds, and if extracts of these molds are used in treatment along with ragweed the results are improved. For some reason, molds appear to be more important for treatment of children than they are for treatment of adults.

It is necessary to know much more about the molds. The trouble is that the study is immensely difficult. Once more I have to call attention to an observation which was made in the allergy clinic of the Massachusetts General Hospital in 1938.[62] A plant pathologist engaged in the study of the fungous disease which injures tomato plants acquired sensitiveness to the mold Cladosporium fulvum Smith. Skin tests with

62. Rackemann, F. M.; Randolph, T. G., and Guba, E. F.: The Specificity of Fungous Allergy, J. Allergy **9**:447, 1938.

the extracts of this mold gave positive reactions. At the same time other tests were made, closely related species of the Cladosporium genus being used, and it was found that whereas the patient showed slight reactions to these other species the degree of sensitiveness was much smaller. Here then was evidence of a strict specificity not only to a genus of molds but to a particular species within that genus. My colleagues and I treat our patients with an extract of a stock culture of the mold Alternaria or perhaps Hormodendrum or Aspergillus, and occasionally the results are good. Is it not possible that with better methods of selection of the molds to be used our results might be much better? Studies of the incidence of air-borne molds show a tremendous number of varieties and species, with a predominance of this or that mold depending on factors which are not clear. Harsh and Allen [63] studied the fungous contaminants of the air of San Diego, Calif., and pointed out that the count of molds which grew on exposed nutrient plates was quite different from the count of mold spores which fell on greased slides. In another paper Harsh [64] proposed a mathematical formula for determining the importance of any one species. From Brazil has come a report on air-borne molds by Passarelli and others.[65] A good review of the literature on molds is one by Morrow and Lowe.[66]

On pollens, too, more study is needed to determine the actual specificity of the different varieties or, on the other hand, to show that there is enough crossed relationship between these species to justify the present comfortable conclusion that treatment with one or two of the common grasses, for example, is enough "to take care of" all the grasses at the same time. Chobot and Dundy [67] have sought for the cause of hay fever which occurs between the grass and the ragweed season in New England. Skin tests were made with a variety of odd and unusual pollens, and a number of positive reactions were observed, but on account of the discrepancy between skin tests and history these reactions did not help much in the evaluation of the importance of any one pollen. At the present time, there are only two crude methods of selection. One is the history, to indicate the dates as accurately as possible. The other is a field survey augmented by pollen slides to

63. Harsh, G. F., and Allen, S. E.: A Study of Fungus Contaminants of the Air of San Diego and Vicinity, J. Allergy **16**:125, 1945.

64. Harsh, G. F.: Pollinosis in San Diego County, California, with a Proposed Method for the Estimation of the Relative Importance of the Plants Concerned, Ann. Allergy **3**:27, 1945.

65. Passarelli, N.; de Miranda, M. P., and de Castro, C.: Mold Studies in Rio de Janeiro, Rev. med.-cir. do Brasil **52**:173, 1944.

66. Morrow, M. B., and Lowe, E. P.: Molds in Relation to Asthma and Vasomotor Rhinitis, Mycologia **35**:638, 1943.

67. Chobot, R., and Dundy, H. D.: The Causes of Hay Fever Occurring Between the Grass and Ragweed Season, J. Allergy **15**:182, 1944.

make sure that the suspicion about any particular plant can be supported by showing that it is capable of producing pollen in reasonable quantity and that the particular patient has probably been exposed to it.

As for surveys of pollen, it is interesting to have Greco [68] state that in Brazil the grasses are the chief offenders and that the pollenating season occurs from the middle of May to the end of June. This is surprising because in the southern latitudes May and June would correspond to November and December in the northern latitudes; it would be the fall rather than the spring season.

The mechanism of hay fever and the technic of specific treatment are problems of primary importance, because pollen sensitiveness is the simplest form of allergy and it concerns thousands of patients who suffer. In 1935, Cooke, Barnard, Hebald and Stull [69] first presented evidence for an antibody in hay fever which could block the union of ragweed with the ordinary sensitizing antibody called reagin. Since then, the study of this blocking antibody has been continued by Loveless.[70] She has developed a technic for measuring the amount of this blocking antibody, and she can show that the amount is proportional to the degree of improvement in symptoms following treatment. There are two kinds of antibodies in hay fever. The sensitizing antibody is thermolabile, destroyed by heating to 56 C., while the blocking antibody is thermostabile and resistant to heat for a long time. If there are two antibodies then there must be two separate antigens, and this fits in with the conclusions which Newell [71] reached in 1942, that it was impossible to purify the extract of ragweed by physical means. All the different fractions which he could separate by precipitation with ammonium sulfate or with alcohol gave positive reactions in skin tests on patients sensitive to ragweed.

Whether the concentration of the thermostabile antibody is always proportional to the degree of clinical relief from symptoms of hay fever is still debatable. Loveless [72] said that it is. Cooke,[73] however, found

68. Greco, J. B.: Pollen Studies in Brazil: Pollen Counts in Eleven Brazilian Cities, Rev. med.-cir. do Brasil **52**:95, 1944.

69. Cooke, R. A.; Barnard, J. H.; Hebald, S., and Stull, A.: Serological Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever), J. Exper. Med. **62**:733, 1935.

70. Loveless, M. H.: Immunological Studies of Pollinosis: I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients, J. Immunol. **38**:25, 1940.

71. Newell, J. M.: A Review of Chemical Studies on the Allergens in Pollens, J. Allergy **13**:177, 1942.

72. Loveless, M. H.: Immunologic Studies of Pollinosis: VI. Shortening the Treatment of Hay Fever, J. Allergy **15**:311, 1944.

73. Cooke, R. A.: A Consideration of Some Allergy Problems: II. Serologic Studies of the Skin-Reacting Allergies (Hay Fever Type), J. Allergy **15**:212, 1944.

that it is not. Gelfand and Frank [74] studied 34 cases. High antibody titers did not always go with high total dosage, and then, more important, high titers were not accompanied with good clinical results in every case. Cohen and Friedman [75] treated normal persons with a 10 per cent extract of ragweed in repeated doses and then collected their serum globulin, which was found to contain considerable quantities of the thermostabile blocking antibody. To this globulin was added amounts of ragweed extract sufficient to combine completely with the antibody, and then patients were treated with this neutralized antigen. A rise in the titer of the thermostabile antibody was produced. In a discussion of this paper, Loveless noted that the neutralized antigen had produced local and general reactions, showing that the combination was not too stable. It was, however, capable of exciting production of the antibody, but the end results in 31 patients were no better or worse than was the ordinary treatment with ragweed extract by itself. The method is a little different from that of mixing the patient's own sensitive serum with ragweed extract so as to neutralize the skin-sensitizing antibody and then giving the mixture back again. Tuft [76] said that he tried this and the results were disappointing. To me it would seem like an interesting experiment, and it might be worth trying again. Incidentally, Johnson and her associates [77] in Alexander's laboratory have with a special technic demonstrated the formation of a precipitate when ragweed extract was added to the serum of treated patients, and the fact supports the antibody theory.

Rhinorrhea Due to Chronic Vasomotor Rhinitis.—"Perennial hay fever" is a troublesome disease, which may be serious. It is included in the conditions dependent on the asthmatic state chiefly because it is associated with other and more typical manifestations and partly because it has eosinophile cells in the nasal secretion. There are two interesting facts about it. One is that when it occurs in young women in their twenties or early thirties and becomes severe it may develop into asthma, which thereupon becomes persistent and severe and may be fatal. This appears to be almost a separate disease, and it deserves much more study. I hope that if others find cases they will report them.

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74. Gelfand, H. H., and Frank, D. E.: Studies on the Blocking Antibody in Serum of Ragweed-Treated Patients: II. Its Relation to Clinical Results, J. Allergy **15**:332, 1944.

75. Cohen, M. B., and Friedman, J.: Treatment of Ragweed Pollinosis with Antigen-Antibody Mixtures: Preliminary Report, J. Allergy **16**:121, 1945.

76. Tuft, L.: Critical Evaluation of Skin Tests in Allergy Diagnosis, J. Allergy **14**:355, 1943.

77. Johnson, M. C.; Alexander, H. L.; Robinson, R., and Alexander, J. H.: A Quantitative Method for Measurement of Precipitin Reactions, J. Allergy **15**: 83, 1944.

The second fact is that treatment by the use of local drops to the nose may do more harm than good. In particular, the drug called Privine (2-naphthyl-1-methylimidazoline hydrochloride) is especially vicious. At first the effect seems to be "wonderful," but soon the patient and the doctor find that the more is used the more is needed. In 1943 Fabricant and Van Alyea [78] advised it, and, in 1944, Craver, Chase and Yonkman [79] described its action. In their book (1944) Feinberg and Durham [80] recommended Privine, but now Feinberg and Friedlaender [81] have recognized its dangers. Since then, Thomas [82] has also called attention to the harmful effects of Privine, and I, too, have "cured" several patients by insisting that they abstain from nose drops of every kind. The reason for the trouble with Privine is not yet clear. Skin tests are not helpful.

ASTHMA

When asthma of any kind becomes severe it is apt to be associated with an increase in the white cell count and particularly in the eosinophile cells. One has learned to regard eosinophilia as of bad prognostic import, for apparently it occurs especially in the cases of severe asthma. In 1939 Rackemann and Greene [83] presented 8 cases of periarteritis nodosa which had occurred in patients with severe asthma. Since then other patients have been suspected of having the same condition, although their symptoms were not so definite; the diagnosis could not be proved.

Now come two other diagnoses which deserve study in connection with severe asthma and periarteritis nodosa. Loeffler's syndrome is one, and in the lungs are found transient consolidations, which come and go in patients who have been sick for a number of months with what appears to be a disease of moderate severity, although persistent. At Camp Blanding, in twelve months Wright and Gold [84] saw 26 cases of Loeffler's syndrome. The patients had blood eosinophilias which

78. Fabricant, N. D., and Van Alyea, O. E.: A Note on the Evaluation of Privine HCl as a Nasal Vasoconstrictor, Am. J. M. Sc. **205**:122, 1943.

79. Craver, B. N.; Chase, H. F., and Yonkman, F. F.: Pharmacologic Studies of a New Vasoconstrictor: 2-Naphthl-(1')-Methyl-Imidazoline Hydrochloride (Privine or Naphthazoline), J. Pharmacol. & Exper. Therap. **82**:275, 1944.

80. Feinberg, S. M., and Durham, O. C.: Allergy in Practice, Chicago, The Year Book Publishers, Inc., 1944, p. 502.

81. Feinberg, S. M., and Friedlaender, S.: Nasal Congestion from Frequent Use of Privine Hydrochloride, J. A. M. A. **128**:1095 (Aug. 11) 1945.

82. Thomas, J. W.: Paper read before the American Academy of Allergy, Chicago, Dec. 10, 1945.

83. Rackemann, F. M., and Greene, J. E.: Periarteritis Nodosa and Asthma, Tr. A. Am. Physicians **54**:112, 1939.

84. Wright, D. O., and Gold, E. M.: Loeffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis), J. A. M. A. **128**:1082 (Aug. 11) 1945.

ranged up to 32 per cent, and in the sputum eosinophils constituted 90 per cent of the cells found. In Miller's [85] case the eosinophilia varied from 60 to 85 per cent during the first two months and then returned to normal after treatment with oxophenarsine hydrochloride. (Note the drug used.) Smith's [86] patient was a woman (aged 55) whose white cell count was 20,000, with eosinophils 49 per cent. A roentgenogram showed extensive shadows involving the whole right lung, but two weeks later another plate showed the area clear. Jones and Carlton [87] have discussed such causes as tuberculosis, intestinal parasites, brucellosis and trichinosis, without being able to incriminate any one. Hansen-Pruss and Goodman [88] observed 6 cases; the diseases were mostly in young persons, and all the patients had high eosinphilias.

Closely related is the condition called "tropical eosinophilia." It was described first by Weingarten,[89] who had made the diagnosis in India and found that the disease was not uncommon in the tropics. It runs a slow course, and the patients are not too sick. This disease may last for months or years, and asthma is an important feature of the symptoms. Here again is a high white cell count, with eosinophils reaching 70 to 80 per cent. During this year there are a number of new reports on tropical eosinophilia. Emerson [90] observed a young ensign who had had sinusitis and asthma before the war. In India he was completely well for four and one-half years, and then quite suddenly came asthma again, after a mild infection in his eyelid. His white cell count ranged from 15,000 to 20,000, with eosinophils from 15 to 20 per cent. A hepatic abscess was found and drained, and after that the white cell count rose to 32,500, with eosinophils to 78 per cent. The diagnosis of tropical eosinophilia was made, and treatment with carbarsone, in doses of 0.25 Gm. by mouth twice a day for two periods of ten days each, cured him. Did the asthma depend on his asthmatic background? The case reported by Hirst and McCann [91] was that of another naval officer in whom asthma also developed suddenly while the patient was in the Pacific Area. For a whole year he had asthma off and on until finally he was found to have a white cell count of 15,500, with eosinophils up to 72 per cent. His sputum was loaded

85. Miller, H.: Transitory Lung Infiltrations Accompanied by Eosinophilia, New England J. Med. **232**:7, 1945.

86. Smith, J. H.: Loeffler's Syndrome, South. M. J. **36**:269, 1943.

87. Jones, S. H., and Carleton, R. S.: Eosinophilic Infiltration of the Lungs (Loeffler's Syndrome), New England J. Med. **231**:356, 1944.

88. Hansen-Pruss, O. C., and Goodman, E. G.: Allergic Pulmonary Consolidations, Ann. Allergy **2**:85, 1944.

89. Weingarten, R. J.: Tropical Eosinophilia, Lancet **1**:103, 1943

90. Emerson, K.: Tropical Eosinophilia, U. S. Nav. M. Bull. **42**:118, 1944.

91. Hirst, W. R., and McCann, W. J.: Tropical Eosinophilia: Report of Case, U. S. Nav. M. Bull. **44**:1277, 1945.

with eosinophils. No parasites could be found. The administration of neoarsphenamine by vein, five doses given four days apart, cured him.

Apley and Grant [92] have put together four conditions: intrinsic asthma, periarteritis nodosa, Loeffler's syndrome and tropical eosinophilia. They have many features in common. They have slow chronic courses, no obvious etiology, asthma in each one—though not asthma in every case of periarteritis nodosa—and eosinophilia. Apley and Grant referred to them as representing the "EP syndrome," which means eosinophilia with pulmonary disease. In tropical eosinophilia, the administration of arsenic in the form of carbarsone by mouth or neoarsphenamine or oxophenarsine hydrochloride by vein is a treatment which is almost specific for the disease. The effect is remarkable, and the patient recovers promptly when arsenic is administered. In the other conditions there has been no such good treatment, but, on the other hand, arsenic has not been tried in these other conditions, at least not in a series of reported cases. Does arsenic have any effect on Loeffler's syndrome or on periarteritis nodosa or even on intrinsic asthma? It would seem proper to try arsenic. In case the drug is not effective in these other conditions, then it would seem proper to distinguish tropical eosinophilia from them. If, on the other hand, arsenic does benefit, then one could enlarge one's concept and regard the four states as variations of the same fundamental disease.

"All is not allergy that wheezes," and one finds more and more recognition of the fact that the cause of asthma may be something which the patient carries with him and that it has nothing to do with sensitiveness to foods or to dusts in the environment. Cohen,[93] in discussing the classification, gave no figures, but he stated that the cases are about equally divided between extrinsic and intrinsic asthma. Leopold [94] studied 200 soldiers returned from overseas because of severe asthma. Most of them had been in the tropics, and the trouble began there. In 69 per cent there was a history of asthma prior to enlistment, and this is further support for the "asthmatic state" described at the beginning of this review. In 88 per cent of Leopold's cases the climate alone, perhaps aggravated by dust or infection, was described as the precipitating factor.

As for diagnosis, Swineford and Weaver [95] have commented once more on the importance of a good clinical history as well as on the

92. Apley, J., and Grant, G. H.: Tropical Eosinophilia, Lancet **1**:812, 1945.

93. Cohen, M. B.: Bronchial Asthma: Classification Based on Etiological and Pathological Factors, Ann. Int. Med. **20**:591, 1944.

94. Leopold, H. C.: Study of Asthmatics Returned from Overseas, J. Allergy **16**:30, 1945.

95. Swineford, O., and Weaver, W. M.: History Taking in Allergy: An Outline for and a Comparison of Results from Two Hundred Histories and Skin Tests, Ann. Int. Med. **20**:293, 1944.

discrepancies between history and skin tests, which are so common. Out of 355 patients with positive histories of clinical sensitiveness, only 70 had positive reactions in skin tests to go with the histories. In 285 the reactions to the skin tests remained perfectly negative. In his presidental address before the Society for the Study of Asthma and Allied Conditions, Tuft [76] also laid stress on the history, in his discussion of the difficulties and the pitfalls in relying too heavily on skin tests. Meantime, Oliveria Lima [96] has given figures for the results of skin tests made on 5,000 allergic patients. Such items as milk, eggs, wheat, rice, tomato and chocolate elicited reactions in from 10 to 42 per cent of the cases. Pollen and fungi were also frequent positive reactors. One wonders whether figures from other clinics would give anything like the same results.

When one distinguishes between extrinsic and intrinsic asthma, the age of onset is of almost primary importance. When the age of onset is below 30, the chances are that the asthma is due to allergy, that is extrinsic. If the asthma began in childhood, it is almost sure to depend on allergy. When, however, the onset of asthma is after a patient has reached the age of 40, then the chance of allergy is much smaller. The use of this principle may be illustrated by the case reported by Wiseman and McCarthy-Brough.[97] An old widow, of 78 years, weighing only 75 pounds (34 Kg.), died within fifteen minutes after a skin test had been done by the intradermal method. If it had been appreciated that her asthma had begun in childhood, at the age of 4, more attention might have been paid to the possibility of sensitiveness.

Treatment of Asthma.—Penicillin has been used for treatment of asthma, particularly for that which is thought to be on a basis of bacterial infection. Leopold and Cooke [98] reported the cases of 2 women. The first received over 1,250,000 units, as a result of which violent urticaria with fever developed with "all of the essential characteristics of serum disease [which] persisted for 6 days." After that the asthma cleared and she was free for three months, but then in October came a new cold and asthma recurred. At that point she was given sulfadiazine for a few days, and after this second treatment she stayed well. The condition of the second woman responded with less violence and more satisfaction. She was given 100,000 units of penicillin every day for ten days, after which her asthma cleared and she remained well during

96. Oliveira Lima, A.: A Statistical Study on the Incidence of Intradermal Tests in Five Thousand Allergic Patients, Rev. med.-cir. do Brasil **52**:1, 1944.

97. Wiseman, J. R., and McCarthy-Brough, M. P.: Skin Sensitivity in the Aged: Fatality Following the Intradermal Tests, J. Allergy **16**:250, 1945.

98. Leopold, S. S., and Cooke, R. A.: Penicillin in the Treatment of Intractable Bronchial Asthma: A Preliminary Report, Am. J. M. Sc. **209**:784, 1945.

the five months of observation. Hampton and his co-workers [99] treated 9 patients with intrinsic asthma with penicillin, but slight improvement occurred in only 4 of the 9 patients. It is the opinion of Hampton and his colleagues that penicillin was of little or no value and offered no advantage over other types of therapy in the treatment of intrinsic asthma. Schonwald and Deppe [100] treated 86 patients with the broth filtered from a culture of Penicillium notatum and caused pronounced improvement in 34 of them. Penicillin does good only when the drug reaches the bacteria and reaches it in sufficient quantity. Vermilye [101] had a good idea when he placed a strong solution of sodium penicillin, 25,000 units per cubic centimeter, in a Vaponephrin Nebulizer and then connected the apparatus with an oxygen tank to lead oxygen through the liquid and make the patient inhale all of it. With this method the blood concentration could be maintained up to 0.40 units per cubic centimeter. He found the method useful not only in acute primary infections of the bronchi and lungs but in chronic infections as well. With the fine "Aerosol spray" the penicillin is in fact brought into contact with the organisms and so can be expected to be effective.

Reactions to penicillin are all too common. "Serum disease" has occurred in a number of cases. The patients of Leopold and Cooke [98] have been mentioned. In Lamb's [102] first patient there developed on the fifth day on the genitals and fingers a vesicular eruption, which coalesced later and became eczematous. His second patient had a similar vesicular eruption on his extremities. It is interesting that in both cases the omission of the penicillin was followed by exfoliation of the eruption and clearance of the itching within twenty-four hours. In the patient described by Price, McNairy and White [103] asthma and giant hives developed on the twelfth day after intensive treatment of his syphilis with penicillin. The reaction was severe, for asthma recurred on the fifteenth day and the boy was almost dead. However, after treatment with oxygen, epinephrine and 50 per cent dextrose intravenously he recovered promptly and was discharged on the eighteenth

99. Hampton, S. F.; Wine, M. B.; Allen, W.; Thompson, C. S., and Starr, M. P.: The Clinical Use of Penicillin in the Treatment of Intrinsic Asthma, J. A. M. A. **127**:1108 (April 28) 1945.

100. Schonwald, P., and Deppe, E. F.: Penicillium Antibiotic in the Treatment of Intrinsic Allergies, Northwest Med. **44**:10, 1945.

101. Vermilye, H. N.: Aerosol Penicillin in General Practice, J. A. M. A. **129**:250 (Sept. 22) 1945.

102. Lamb, J. H.: Allergic Reactions During the Administration of Penicillin, Arch. Dermat. & Syph. **52**:93 (Aug.) 1945.

103. Price, D. E.; McNairy, D. J., and White, E. L.: Severe Asthma: Delayed Sensitization to Penicillin, J. A. M. A. **128**:183 (May 19) 1945.

day. Lyons [104] found among 209 cases that urticaria appeared in 12 of them (5.7 per cent). It occurred as early as the first day or as late as the fourth week of treatment—quite comparable to the reaction after injection of horse serum. Other types of reaction occur. In a patient of Morris and Downing [105] a bullous dermatitis developed from administration of penicillin.

The possible relation betwen allergy to the fungus Penicillium and reactions to the extract penicillin has been considered by Feinberg.[106] Penicillium spores constitute at least 11 per cent of all the fungous spores in the air. Ten patients sensitive to molds were found to give 3 plus reactions to the spores of Penicillium rubrum and Penicillium notatum, but tests on these same persons with penicillin—the purified extract—elicited a negative reaction. Cormia, Jacobsen and Smith [107] have reported on the reactions to penicillin observed in the treatment of 2,000 soldiers. Mild reactions—mostly transient urticaria—were not uncommon. In only 11 patients out of the 2,000 were the reactions bad enough to require stopping of the treatment.

The sulfonamide drugs have also been used for the treatment of asthma. We ourselves have had some success with the sulfonamide compounds in a few cases. Reactions to the sulfonamide drugs are, however, all too common, and particularly when the drug is used a second time. These reactions vary widely in their character. Drug fever is the common one. Dowling and Lepper [108] found that in 5 per cent of 737 patients fever developed during the second course of treatment. When, however, the particular sulfonamide drug taken in the second course was different from that used in the first course, then in only 3 per cent trouble developed. Disturbances of the blood cells appear to be more characteristic. Thrombocytopenic purpura caused by the sulfonamide drugs has been reported: 3 cases by Gorham and colleagues [109] and 1 case by Meyer.[110] In the latter the platelet count

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104. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, J. A. M. A. **123**:1007 (Dec. 18) 1943.

105. Morris, G. E., and Downing, J. G.: Bullous Dermatitis (Dermatitis Medicamentosa) from Penicillin, J. A. M. A. **127**:711 (March 24) 1945.

106. Feinberg, S. M.: Penicillin Allergy: On the Probability of Allergic Reactions in Fungus-Sensitive Individuals; Preliminary Experiments, J. Allergy **15**:271, 1944.

107. Cormia, F. E.; Jacobsen, L. Y., and Smith, E. L.: Reactions to Penicillin, Bull. U. S. Army M. Dept. **4**:694 1945.

108. Dowling, H. F., and Lepper, M. H.: "Drug Fever" Accompanying Second Courses of Sulfathiazole, Sulfadiazine and Sulfapyridine, Am. J. M. Sc. **207**:349, 1944.

109. Gorham, L. W.; Propp, S.; Schwind, J. L., and Chinenka, D. R.: Thrombocytopenic Purpura Caused by Sulfonamide Drugs: A Report of Three Cases, Am. J. M. Sc. **205**:246, 1943.

110. Meyer, A. H.: Thrombocytopenic Purpura: A Case Caused by Sulfadiazine, California & West Med. **60**:99, 1944.

fell to dangerous levels. A good point is made by Rothendler and Vorhaus,[111] who gave penicillin for prevention of generalized sepsis when the leukocytes were depressed in agranulocytosis.

Cutaneous lesions are also important, and the nature of these varies widely from case to case. Fisher[112] from Australia reviewed 100 cases of dermatitis following the local application of sulfanilamide. The rash usually appeared from two to four days after the start of treatment, sometimes not until the eighth to twelfth day, and then it cleared when the drug was withdrawn. Patch tests elicited positive reactions. Frist[113] gave a review of 186 cases of reactions to sulfonamide drugs. Fever and cutaneous eruptions predominated. A lucid and complete discussion of the nature and the mechanism of reactions from certain drugs, particularly the sulfonamide compounds, may be found in a paper by Longcope,[114] published in *Medicine* in 1943.

The barbiturates may cause trouble in an occasional case. Potter and Whitacre[115] described a patient in whom a chill with fever and generalized erythema developed within a few hours after she had taken 0.1 Gm. of phenobarbital.

Theophylline ethylenediamine (aminophylline) is useful in treatment of severe asthma. It is somewhat effective if given by mouth in doses of 0.2 Gm. four times a day, but much more effective if given by vein in a dose of 0.30 Gm., dissolved in 10 cc. of isotonic solution of sodium chloride. Reactions to theophylline ethylenediamine are not common. Hundreds of injections have been given at the Massachusetts General Hospital, with never any serious difficulty, but we are careful to give the injections slowly. Waldbott[116] stated that he has given 20,000 injections, with no trouble at all. However, 3 fatalities have been reported by Merrill.[117] Two patients were under treatment for cardiovascular disease and 1 for asthma, and in all 3 death followed immediately after the intravenous administration of theophylline ethylenediamine. The useful method of giving theophylline ethylenediamine

111. Rothendler, H. H., and Vorhaus, M. G.: Penicillin in Thiouracil—Induced Agranulocytosis, J. A. M. A. **129**:739 (Nov. 10) 1945.

112. Fisher, B.: Dermatitis Following the Local Application of Sulfanilamide, M. J. Australia **2**:449, 1944.

113. Frist, I. F.: Reactions to Sulfonamide Compounds: A Review of One Hundred and Eighty-Six Cases, War Med. **5**:150 (March) 1944.

114. Longcope, W. T.: Serum Sickness and Analogous Reactions from Certain Drugs, Particularly the Sulfonamides, Medicine **22**:251, 1943.

115. Potter, J. K., and Whitacre, R. J.: Dermatitis Due to Barbiturates: Report of a Case with Associated Anemia, Ann. Int. Med. **21**:1041, 1944.

116. Waldbott, G. L.: Emergencies in the Allergist's Practice, J. A. M. A. **128**:1205 (Aug. 25) 1945.

117. Merrill, G. A.: Aminophylline Deaths, J. A. M. A. **123**:1115 (Dec. 25) 1943.

by rectum was first proposed by Dees,[118] who treated 49 adults and 6 children with suppositories containing 0.25 Gm. in theobroma oil and wax. Relief of symptoms occurred within twenty minutes, and many epinephrine-fast patients regained their normal response to epinephrine. Barach [119] found that a solution of theophylline ethylenediamine, 0.50 Gm. of the drug dissolved in 20 cc. of water, injected into the rectum through a small catheter is easy and safe.

Demerol (1-methyl-4-phenyl peperidine-4-carbonic acid), a new synthetic, is said to have good spasmolitic and sedative effects without at the same time disturbing the activity of the respiratory center. However, I am skeptical: I believe that sedative drugs of all sorts must be used with great caution in patients with severe asthma. The risk of lowering the activity of the respiratory center and so allowing the patient to suffocate is very real. Morphine should never, in any circumstances, be used in asthma, and the same principle applies to Demerol and all other drugs related to morphine.

Ethylene disulfonate drew a good deal of attention last year. Theoretically, it is a catalyst concerned with enzyme activity, but the quantity advised—a dilution of $1:10^{-15}$—seems absurd. Experiments by Fisk, Small and Foord [120] have shown it to be of no value in the prevention of anaphylactic shock in guinea pigs.

CONDITIONS RELATED TO ALLERGIES

Rheumatoid arthritis, peptic ulcer, colitis and migraine constitute the last line of the diagram in the chart. These are added because there is so much in common between them and the more regular "asthmatic" symptoms. Rheumatoid arthritis may be allergic in the sense of the delayed inflammatory reaction rather than of the immediate urticarial reaction. Rackemann [121] suggested this in 1933, and Aikawa [60] has discussed it again now. However, rheumatoid arthritis is not associated with asthma and hay fever: It is not an "asthmatic" disease. Whereas its fundamental mechanism may be similar in principle, it is not the same. Peptic ulcer and colitis are in the line chiefly because Selye [11] has described gastric hemorrhage as an incident in the alarm reaction and as a result of treating animals with desoxycorticosterone acetate.

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118. Dees, S. C.: The Use of Aminophyllin Rectal Suppositories in the Treatment of Bronchial Asthma, J. Allergy **14**:492, 1943.

119. Barach, A. L.: Rectal Instillation of Aminophylline in Intractable Asthma, J. A. M. A. **128**:589 (June 23) 1945.

120. Fisk, R. T.; Small, W. S., and Foord, A. G.: The Experimental Use of Ethylene Disulfonate (Allergosil Brand) in the Prevention of Anaphylaxis in Guinea Pigs, J. Allergy **15**:9, 1944.

121. Rackemann, F. M.: The Role of Allergy in Arthritis, New England J. Med. **208**:1347, 1933.

Migraine has a better "case." Randolph [122] and Wolf and Unger [123] here, as well as Estiu and Dumm [124] in Brazil, have seen patients with migraine whose symptoms disappeared when particular foods, especially milk, were eliminated from the diet. Such cases are rare. Moreover, headache is not a common accompaniment of hay fever and asthma. Horton and his co-workers [51] have done much to stimulate interest in the relation of the histamine problem to the headache problem. They have been able to relieve a number of patients by treatment of "histaminic cephalalgia" with histamine. Atkinson [125] has described "red" and "white" headaches according to vasodilatation or vasoconstriction, the former being sensitive to histamine. Also he described the relation between Ménière's disease and migraine in a thoughtful discussion. This year Butler and Thomas [126] advised treating migraine by injection of histamine intravenously in a dilution made by adding 1 mg. of histamine base (2.75 mg. of histamine acid phosphate) to 500 cc. of isotonic solution of sodium chloride, to be given slowly. Another interesting paper is by Wolff and Torda,[127] who made studies of the urine before and during the migraine seizure. When the urine was added to a bath containing frog muscle, the muscle contracted greatly with urine passed during the headache but not with urine passed before or after the headache. The other day I saw a patient who suffered from attacks of angioneurotic edema and urticaria of considerable severity. A report on this man showed that in 1930 Dr. George MacKenzie had tested his urine in the Dale apparatus. When urine before the attack was added to the Dale bath, the guinea pig uterus did not react but "there was on two occasions a demonstrable reaction similar to that caused by histamine when the urine passed immediately after an attack was used." Was the urine boiled with acid to destroy such vasodilators as "kallikrein" and adenosine without disturbing the histamine? The technic of these experiments is important. Wolff and Torda quoted Hanke and Koessler [128] as having been unable to find

122. Randolph, T. G.: Allergic Headache: An Unusual Case of Milk Sensitivity, J. A. M. A. **126**:430 (Oct. 14) 1944.

123. Wolf, A. A., and Unger, L.: Migraine Due to Milk: Feeding Tests, Ann. Int. Med. **20**:828, 1944.

124. Estiu, M., and Dumm, J. F.: Allergic Headaches, Rev. med.-cir. do Brasil **52**:23, 1944.

125. Atkinson, M.: Ménière's Syndrome and Migraine: Observations on a Common Causal Relationship, Ann. Int. Med. **18**:797, 1943.

126. Butler, S., and Thomas, W. A.: Intravenous Histamine in the Treatment of Migraine, J. A. M. A. **128**:173 (May 19) 1945.

127. Wolff, H. G., and Torda, C.: Experimental Studies on Headache: Pharmacodynamics of Urine Excreted During Migraine Headache and Its Relation to Seventeen-Ketosteroid Content, J. Clin. Investigation **22**:853, 1943.

128. Hanke, M. T., and Koessler, K. K.: Studies on Proteinogenery Amines, J. Biol. Chem. **43**:521, 1920.

by their colorimetric method histamine in the urine during the headache. When the 17-keto steroids were isolated from the urine passed during the headache they produced a contraction of the muscle, and the finding was interpreted as showing the factors of stress and strain in the disease.

Contact dermatitis is not noted in the diagram and yet it is of considerable practical importance in every allergy clinic. It depends on a sensitiveness which is localized to the skin, sometimes to certain parts of the skin, and which is specific for one out of a great variety and number of offending substances. How does this fit the scheme outlined? Do the persons in whom contact dermatitis develops also have the asthmatic state— the *X*? How many of them gave a history of other allergies at the same time? How many have a family history positive for allergy?

Hall [129] observed 755 employees in the skin clinic of the Douglas Aircraft Corporation and found 202 with occupational dermatitis which was due to zinc chromate in the paint used. Resins were secondary factors. Lockey [130] laid stress on resins and described the varieties. Lane and his co-workers [131] found that dermatoses of the hands were the chief complaint of 9 per cent of 475 new patients coming to the skin clinic. In this group occupational dermatoses were not common; there were only a few cases in which the lesions were due to a specific acquired sensitiveness. The authors stated the belief that bacteria were the important factors and that excessive soap and water as well as excessive medicinal treatment was the cause of most of the trouble. Figures were not given; the problem in each case was too complicated. Grolnick, Bowman and Walzer [132] made an interesting study. They found that when the specific contact dermatitis had subsided a test of the site made by injection of the allergen solution into that skin would result in a wheal formation which was larger than the wheal made at another place on the same patient. This goes along with the description of Lane to indicate that the skin once involved in a contact dermatitis becomes altered in its reaction both to specific and to nonspecific stimuli. Soap and irritants of all kinds are bad for it.

Dermatitis caused by poison ivy is all too common. It has been cited as the borderline between allergic and normal persons to show that the differences are more of degree than of kind. There is one

129. Hall, A. F.: Occupational Contact Dermatitis Among Aircraft Workers, J. A. M. A. **125**:179 (May 20) 1944.

130. Lockey, S. D.: Contact Dermatitis Resulting from the Manufacture of Synthetic Resins and Methods of Control, J. Allergy **15**:188, 1944.

131. Lane, C. G.; Rockwood, E. M.; Sawyer, C. S., and Blank, I. H.: Dermatoses of the Hands, J. A. M. A. **128**:987 (Aug. 4) 1945.

132. Grolnick, M.; Bowman, K. L., and Walzer, M.: Response of Contact Dermatitis Sites in Atopic Individuals to Subsequent Stimulation with Specific Wheal-Inducing Atopens, J. Allergy **16**:188, 1945.

paper on poison ivy which must be read by every one interested. Stevens[133] has made an intelligent review of the entire literature on poison ivy, giving the plain facts concerning the so-called specific treatment. He is not encouraging. Meantime, nothing in these papers or in many others on the same subject is said about the patient who is having the disease. So far, it is my impression that whereas eczema of the "atopic" type—that in children and young adults who have lesions on face and neck and in cubital and popliteal spaces (otherwise called "flexural eczema")—is true to the asthmatic picture contact dermatitis does not belong. Perhaps, however, the distinction depends on degree more than on kind, and when the day comes that the nature of the allergic state (my x) is known and a method of inhibiting it is developed it is probable that even though dermatitis caused by poison ivy and other contact dermatitides do not fit the picture a little treatment for x will do them good.

This review points out that in the development of asthmatic symptoms there are a number of parts or "levels" in the mechanism and that each part is more or less separate from the other. In simple allergy like hay fever, treatment at the middle level of the antigen-antibody reaction itself is the method best known at this time. Even when this treatment is entirely successful for the moment, the person is still allergic: He still has his capacity to develop sensitiveness, and he still has his "asthmatic state." He is "cured" only in the clinical sense, and his cure is only temporary and only relative. If, in the future, more can be known about histamine, how to inhibit its release or how to modify the reaction of the asthmatic person toward histamine, many more patients can be cured but, best of all if the reason for the "asthmatic state" could be understood and if the factor which is inherited by certain persons and which develops in others could be known then the work on allergy would be done.

133. Stevens, F. A.: Status of Poison Ivy Extracts, J. A. M. A. **127**:912 (April 7) 1945.

News and Comment

SAMUEL S. FELS FUNDS MEDICAL RESEARCH LABORATORY BECOMES ASSOCIATED WITH TEMPLE UNIVERSITY SCHOOL OF MEDICINE

An association of the Samuel S. Fels Funds Medical Research Laboratory with the Temple University School of Medicine for research in gastroenterology and internal medicine has been consummated. The Fels Research Laboratory will henceforth be known as the Fels Research Institute of Temple University School of Medicine and will be located in the medical school laboratory building at Broad and Ontario Streets. According to the agreement approved by the representatives of the agencies, the Samuel S. Fels Fund will furnish the laboratory equipment and will finance the research program covering the salaries of members of the staff and the Institute's operating expenses. The Management Committee of the Institute will consist of an equal number of members appointed by the cooperating groups. Members from the Temple University will include: Dr. Robert L. Johnson, President of the University; Dr. William N. Parkinson, Dean of the Temple University School of Medicine; Dr. Charles L. Brown, Head of the Department of Medicine, and Dr. Robert H. Hamilton, Chairman of the Medical School Committee on Research. Members from the Fels Medical Research Laboratory are to be designated by their Board.

Dr. Harry Shay, who has been in charge of the Fels Medical Research Laboratory since its establishment in 1934, will remain as Director of the new institute.

The culmination of the plan just accepted has been made possible through the generosity and foresight of Samuel S. Fels, Philadelphia manufacturer, who has long since had a deep interest in research in many fields. Mr. Fels has had the vision to see the tremendous possibility for improving the well-being of mankind by the application of scientific research technics to human problems.

GENERAL NEWS

Meeting of Mississippi Valley Medical Society.—The eleventh Annual Meeting of the Mississippi Valley Medical Society will be held at the Hotel Jefferson, St. Louis, on September 25, 26 and 27. More than thirty clinical teachers from the leading medical schools will conduct the postgraduate assembly, the entire program of which is planned to appeal to general practitioners. There will be over sixty technical and scientific exhibits, noonday round-table luncheons and a banquet, preceded by a social hour. Dr. Arthur H. Compton, Nobel Prize Laureate and Chancellor of Washington University, will be the principal banquet speaker, together with the presidents of the Illinois, Iowa and Missouri State Medical Societies. All ethical physicians are cordially invited to attend. A detailed program may be obtained from the Secretary, Harold Swanberg, M.D., 209-224 W. C. U. Bldg., Quincy, Ill.

Dr. A. J. Geiger of Yale, Winner 1946 Mississippi Valley Medical Society Essay Contest.—Dr. Arthur J. Geiger, assistant professor of medicine, Yale University School of Medicine, is the winner of the 1946 annual essay contest of the Mississippi Valley Medical Society "for the best unpublished essay on a subject of practical and applicable value to the general practitioner of medicine."

He will receive $100, a gold medal and a certificate of award. Dr. Geiger's subject was "Penicillin Therapy in Subacute Bacterial Endocarditis."

Second prize was awarded to Dr. F. Steigmann of the University of Illinois for his essay, "The Problem of Jaundice in General Practice," and third prize to Dr. Rutherford T. Johnstone of Los Angeles for his essay, "A Basic Approach to the Diagnosis of the Occupational Diseases."

Mississippi Valley Medical Editors' Association Meetings to be Resumed at St. Louis, September 25.—The Mississippi Valley Medical Editors' Association will resume annual meetings at the Jefferson Hotel, St. Louis, September 25, during the meeting of the Mississippi Valley Medical Society. This will be a dinner meeting, with three well known medical editors as speakers. A discussion period will follow each paper. All interested in medical writing are cordially invited to attend. A detailed program may be secured from the Secretary, Harold Swanberg, M.D., 209-224 W. C. U. Bldg., Quincy, Ill.

American Society for Research in Psychosomatic Problems, Inc.—The following officers were elected at the third annual meeting held at the Pennsylvania Hotel, New York city, May 11 and 12, 1946:

Adolf Meyer, M.D., Honorary President (continued)
Edward Weiss, M.D., President
Edwin G. Zabriskie, M.D., Secretary-Treasurer (continued)

Book Reviews

Constitutional Medicine and Endocrinology. By E. Pulay, M.D., A. P. Cawadias, M.D., and P. Lansel, M.D. Volume 1. Price, 10s. 6d. Pp. 99. London: Frederick Muller, Ltd., 1946.

This book, "Constitutional Medicine and Endocrinology," is stated to be the first of a series of mongraphs bearing this title. This volume is made up of a number of essays: "Constitutional Medicine, Metabolism and Endocrinology," "Addisonism or the Hypotonic Symptom Complex," "Pathophysiology of the Blood Picture," "Haemopoiesis and Constitution" and "Clinical Aspect of the Blood Sedimentation Rate."

The first essay by Cawadias is a thoughtful presentation, although unnecessarily verbose. The thesis is that constitutional medicine is a branch of internal medicine distinct from such subspecialties as cardiology and dermatology. It has to do with what are generally considered metabolic and endocrinologic disorders. It is concerned with the organism or patient as a whole. Its virtue would appear to consist of an emphasis on an approach to the chemical reactions of the body as a whole, and an integration of them. The remainder of the essays have very little to recommend them. They are replete with such pseudoscientific statements as, "Many cases of adrenal-cortex deficiency are to be expected from a lack of vitamin (fruit)" or ". . . many cases of asthmatic attacks are interrelated with hypoglycemia due to hepatic disorders caused by pituitary insufficiency."

The development of a broader concept in constitutional medicine is an attractive possibility. However, the essays in this volume chosen to illustrate this conception are very discouraging. This is a disappointing book.